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SYMPOSIUM ON ANESTHESIA

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THE INFLUENCE OF CERTAIN DRUGS AND ANESTHETICS ON GASTRO-INTESTINAL TONE AND MOTILITY
J. Dewey Bisgard, M.D., and E. K. Johnson, M.D., Omaha, Neb.

THE ASSAY OF ANESTHETIC AGENTS
Henry K. Beecher, M.D., Boston, Mass.

TRENDS IN INHALATION ANESTHESIA
Wesley Bourne, M.D., Montreal, Canada

ANOXIA: A SOURCE OF POSSIBLE COMPLICATIONS IN SURGICAL ANESTHESIA
R. D. McClure, M.D., F. W. Hartman, M.D., J. G. Schnedorf, M.D., and V. Schelling, Ph.D., Detroit, Mich.

THE PRESENT STATUS OF SPINAL ANESTHESIA
Harold L. Foss, M.D., Danville, Pa.

THE EVOLUTION OF SPINAL ANESTHESIA IN ABDOMINAL SURGICAL PROCEDURES
Roscoe R. Graham, M.D., Toronto, Canada

FURTHER EXPERIENCES IN THE USE OF SPINAL ANESTHESIA FOR THORACOPLASTY
F. B. Gurd, M.D., A. M. Vineberg, M.D., and Wesley Bourne, M.D.
Montreal, Canada

INTRAVENOUS AND REGIONAL ANESTHESIA
John S. Lundy, M.D., Rochester, Minn.

THE USE OF SYMPATHETIC NERVE BLOCK ANESTHESIA IN MINIMAL RESECTION OF THE STOMACH FOR ULCERS OF THE PYLORIC ANTRUM AND DUODENUM
William F. Rienhoff, Jr., M.D., Baltimore, M.D.

TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD AT HOT SPRINGS, VA.

MAY 11, 12, 13, 1939

(*Continued*)

THE INFLUENCE OF CERTAIN DRUGS AND ANESTHETICS UPON GASTRO-INTESTINAL TONE AND MOTILITY*

J. DEWEY BISGARD, M.D., AND E. K. JOHNSON, M.D.

OMAHA, NEB.

FROM THE DEPARTMENTS OF SURGERY AND PHYSIOLOGY, UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE, OMAHA, NEB.

POSTANESTHETIC and postoperative disturbance of gastro-intestinal activity manifests itself by nausea and vomiting, by distention from gastric and intestinal dilatation and by gas-pains. With the exception of the immediate postoperative nausea and vomiting, the signs and symptoms of gastro-intestinal dysfunction are attributed by most pharmacologists and surgeons solely to factors unrelated to anesthesia, such as operative trauma to tissues, toxemia, "air swallowing," and postoperative medication. Disturbances resulting from such complications, as mechanical pyloric and intestinal obstruction and ileus associated with peritonitis, are excluded from this discussion.

Unquestionably, surgical trauma is the principal causative factor of postoperative gastro-intestinal symptoms, but the results of the clinical and experimental studies which follow indicate that anesthetics play much more important rôles than are generally attributed to them. These studies also show that some anesthetic agents are inhibitory and others are predominantly motor stimulating to the gastro-intestinal tract, and that those with inhibitory action are associated with disturbances of gastric and intestinal functions much more frequently and that the symptoms of such disturbances are, on the whole, more severe and of longer duration. Also from the studies, there evolved some evidence that the differences in the effects of the two types of anesthetic agents upon the gastro-intestinal tract may be related to their respective influences upon the oxygen saturation of the blood.

As recorded in Table I, an analytic study was made of 408 cases which had had celiotomies with uncomplicated convalescences. These cases were per-

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

sonally observed, either directly or indirectly, and specific records of nausea and vomiting, distention and "gas-pains" maintained and accumulated for the purpose of this study.

The tabulated results show a very impressive difference in the response of gastric and intestinal activity to the various forms of anesthetics indicating the important rôle played by these agents. Sixty-one per cent of cases operated upon with avertin (60 to 90 mg. per Kg. of body weight) -cyclopropane anesthesia never vomited following operation as compared with only 4 per cent with ether, 4.5 per cent with nitrous oxide and ether, 10 per cent with nitrous oxide alone, 20 per cent with cyclopropane alone and 32 per cent with spinal. Similarly, vomiting persisted longer than 24 hours in only 1.3 per cent of cases anesthetized with avertin-cyclopropane as compared with 10 per cent with ether, 14 per cent with nitrous oxide-ether, and 2.2 and 2 per cent with spinal and cyclopropane alone, respectively. There was slight or no distention with avertin-cyclopropane in 50 per cent of cases as compared with only 27 per cent with ether, 30 per cent with nitrous oxide alone or with ether, 40 per cent with spinal and 25 per cent with cyclopropane alone. Distention was persistent and troublesome in no case which received avertin-cyclopropane, in only 1 per cent of cases given spinal anesthesia and in 3 per cent given ether alone or in combination with nitrous oxide. Persistent and troublesome gas-pains occurred in only 1.3 and 2.3 per cent of cases given avertin-cyclopropane and spinal anesthesia, respectively, as compared with 10, 9, 8, and 3 per cent in those given nitrous oxide, nitrous oxide-ether, cyclopropane and ether, respectively. Thus it is apparent that the addition of avertin greatly reduced the symptoms of gastric and intestinal dysfunction and that spinal anesthesia exerted only slightly less favorable influence than did avertin-cyclopropane.

There are, however, a few misleading facts. Nausea and vomiting which occurred in the operating room and before the patients returned to their rooms was not recorded. Consequently some cases credited as never having vomited retched or vomited in the operating room. Included are a few cases given spinal anesthesia, which vomited during operation, and several given gas anesthesia, which vomited upon regaining consciousness in the operating room. However, this included no cases which received cyclopropane as a supplement to a basal anesthesia of avertin and it is in this group that the least disturbance of gastric and intestinal activity occurred.

Also misleading is the fact that there were many children in the groups which received ether, nitrous oxide and combined nitrous oxide and ether. Since children vomit with less provocation and more persistently than adults, the figures in these groups are disproportionately unfavorable. Also, children, as a rule, have less distention and gas-pains postoperatively, giving disproportionately favorable figures in this respect in these same groups.

Aside from these minor discrepancies, the cases in the various groups were relatively comparable and received comparable operative trauma and pre-

TABLE I

CORRELATION OF TYPE OF ANESTHESIA WITH SIGNS AND SYMPTOMS OF GASTRIC AND INTESTINAL DYSFUNCTION IN 408 CASES WITH UNCOMPLICATED CELIOTOMIES

		Nausea and Vomiting*								Distention						Gas-Pains					
Anesthetic	Cases	None	Per Cent	Less Than 12 Hrs.	Per Cent	Gastric Drainage	Per Cent	Persisting After 24 Hrs.	Per Cent	Slight or None	Per Cent	Moderate	Per Cent	Persistent or Severe	Per Cent	None	Per Cent	Slight or Moderate	Per Cent	Severe	Per Cent
Ether	72	3	4	46	64	23	32	7	10	20	27	50	70	2	3	10	14	60	83	2	3
Nitrous oxide-oxygen	10	1	10	6	60	3	30	0	0	3	30	7	70	0	0	1	10	8	80	1	10
Nitrous oxide plus ether	65	3	4.5	45	69.5	17	26	9	14	20	30	43	67	2	3	10	15	49	76	6	9
Cyclopropane	102	21	20	62	62	18	18	2	2	25	25	73	73	2	2	4	4	90	88	8	8
Spinal–novocain, pantocaine	85	28	32	64	58.5	8	9.5	2	2.2	34	40	50	59	1	1	11	13	72	84	2	2.3
Cyclopropane plus avertin	74	45	61	24	32.5	5	6.5	1	1.3	37	50	37	50	0	0	8	11	65	87.7	1	1.3
Totals	408																				

* Patients vomiting more than two or three times and longer than ten hours placed routinely on continuous gastric drainage (suction).

and postoperative care. Since the differences in the late as well as early symptomatic manifestations of dysfunction were so great, it would appear that anesthesia exerted a prolonged as well as transitory influence upon the gastro-intestinal tract.

Experimental Data.—Direct observations of gastric and intestinal motor activity were made during, and for varying periods following, anesthesia in both humans and dogs.

Activity of the stomach and bowel was recorded upon continuous kymographic records which registered pressure changes upon inflated balloons fastened to the ends of indwelling Levine tubes. In the human subjects, the tubes (double Miller-Abbott) were swallowed and were retained either in the stomach or permitted to pass into the small bowel. The location of the tubes was determined radiographically.

In the dogs, the tubes with their balloons were passed into permanent fistulae of the stomach, small intestine and colon. The stomach was entered through a long tube fashioned from its greater curvature (Pavlov pouch), the large bowel through an appendicostomy and the small bowel through an ileostomy leading into a Thery-Vella type of isolated loop of ileum. Records were made during (1) a preanesthetic control period; (2) induction of anesthesia; (3) full surgical anesthesia; (4) a recovery period of one hour or more; and (5) varying postanesthetic intervals, some extending over periods of three days.

Since the muscular activity of the gastro-intestinal tract normally varies greatly from day to day and from minute to minute, the changes in tone and peristaltic activity which take place during a period of experimental observation can be interpreted as responses to experimental factors only if they are constantly repeated under the same circumstances.

Studied were the actions of a few representative drugs used in the pre- and postoperative care of patients and a few representative anesthetic agents. The results are summarized under their respective headings:

I. Motor Effects.

(1) Morphine—16 mg. subcutaneously (Chart I).

(a) Man. The action of morphine upon both the stomach and small bowel was constantly motor in three observations. In each viscus there was a marked increase of tone; in the stomach an increase in the frequency and amplitude of peristaltic contractions and in the small bowel a diminution of amplitude. The effect became apparent in approximately five minutes and after 30 minutes slowly regressed to assume relatively normal tone and activity within an hour after administration.

(b) Dog. In two dogs, observations of the stomach, ileum and colon were made simultaneously. Both animals vomited within five minutes, the retching being immediately preceded by an increase in gastric tone and muscular activity. The tone remained increased for two hours. Gastric con-

tractions were greatly diminished in both frequency and amplitude for approximately two hours and were still somewhat diminished six hours after administration of the drug. Both small bowel and colon showed the same effects; namely, increased tone and diminished muscular activity, but in both there was an earlier return to normal, the ileum in three hours and the colon in two hours.

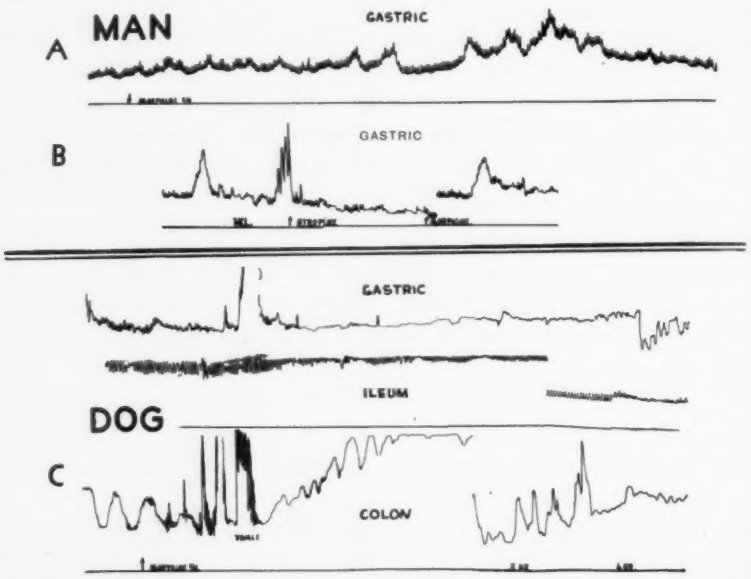


CHART 1.—(A) Action of morphine (16 mg.) upon a normal fasting human stomach. Note progressive increase of tone and of frequency and amplitude of contractions. (B) After inducing hunger contractions by administration of dilute hydrochloric acid to a fasting human stomach atropine (0.65 mg.) caused relaxation and inhibition. Following administration of morphine (16 mg.), the effect of atropine was counteracted and normal tone and contractions reestablished. (C) Simultaneous records of stomach ileum and colon of dog showing normal tracings before morphine (16 mg.) was given subcutaneously, exaggerated excursions accompanying vomiting following its administration, and then the progressive increase in tone with diminution of frequency and amplitude of contractions. Observations three and six hours later show normal tone but still diminished contractions.

(2) Pitressin—ten minims to 1 cc. subcutaneously (Chart 2).

(a) Man. In three subjects, pitressin caused a great increase in both frequency and amplitude of the peristaltic contractions of the stomach but no change in tone. After a brief preliminary lessening of tone and activity both tone and peristalsis were greatly increased in the ileum and the amplitude of the rhythmic contractions was diminished. The effect lasted not longer than 20 minutes.

(b) Dog. The stomach was uninfluenced and the small bowel showed an increase of tone only. In the large bowel both tone and peristalsis were definitely increased. As in man the effect was of short duration.

(3) Dilute hydrochloric acid—20 minims orally (Chart 2).

(a) Man. In three of four patients dilute hydrochloric acid excited the fasting stomach to increased activity, both in respect to frequency and amplitude of peristaltic contractions.

II. Inhibitory Effects.

(1) Atropine—Charts 3 and 5.

(a) Man—0.65 mg. subcutaneously. In both stomach and small bowel there was a marked diminution of tone and of the frequency and amplitude of contractions for approximately an hour and one-half. For 30 minutes peristalsis was entirely abolished in the ileum.

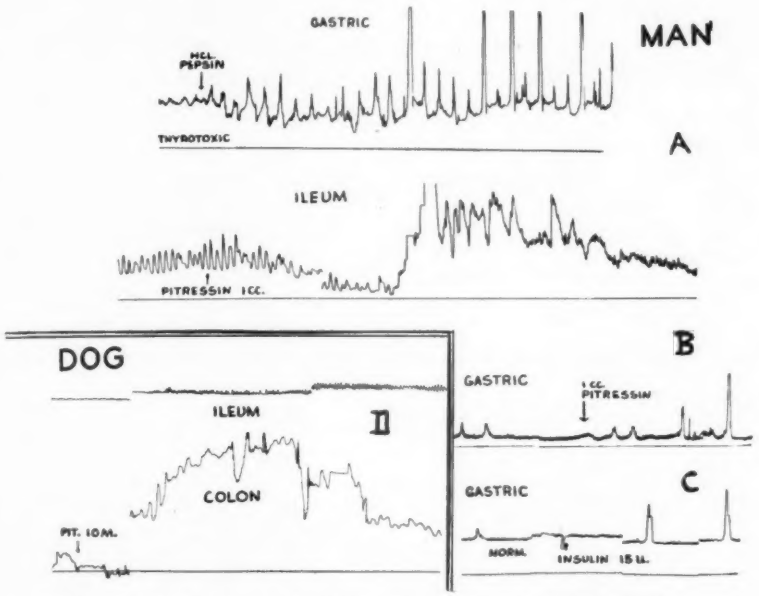


CHART 2.—(A) Action of hydrochloric acid upon normal fasting human stomach. Note reduction of tone with contractions increased in frequency and greatly increased in amplitude. (B) Pitressin (1 cc.) caused in the normal human ileum a preliminary reduction of tone and activity followed by greatly increased tone and peristaltic activity, particularly amplitude. In the stomach there was no change in tone but increase in the amplitude of contractions. (C) Fifteen units of insulin caused the normal fasting stomach to show contractions increased both in frequency and amplitude. (D) Action of pitressin (10 minims) in the dog caused a slight increase of tone and of frequency of rhythmic contractions of the ileum and a large increase in tone and peristaltic activity in the colon.

(b) Dog—0.65 mg. subcutaneously. In three animals, atropine produced no appreciable effect upon the tone and activity of the stomach and small bowel. The colon became relaxed and the activity diminished but not abolished. The effect lasted for approximately one hour.

(2) Nitroglycerine—0.65 mg. (Chart 3).

(a) Man. Observations carried out in two subjects showed that nitroglycerine dissolved under the tongue had transitory inhibitory actions upon both the stomach and ileum. The tone was greatly diminished and the peristaltic activity lessened in both frequency and amplitude, but not abolished. The effect lasted approximately 20 minutes. In two of the patients, hunger contractions had been induced before the administration of nitroglycerine by dilute hydrochloric acid.

(b) Dog—0.43 mg.

As observed in one dog, the action of nitroglycerine upon the stomach, ileum, and colon was identical to that observed in man as described above.

(3) Seconal—195 mg. (Chart 3).

(b) Dog. In two animals, this drug had no definite effect upon the stomach but was markedly inhibitory to the ileum and colon. Tone in both portions of the gut was markedly reduced and muscular activity of the large bowel was almost entirely abolished. Although the ileum continued to con-

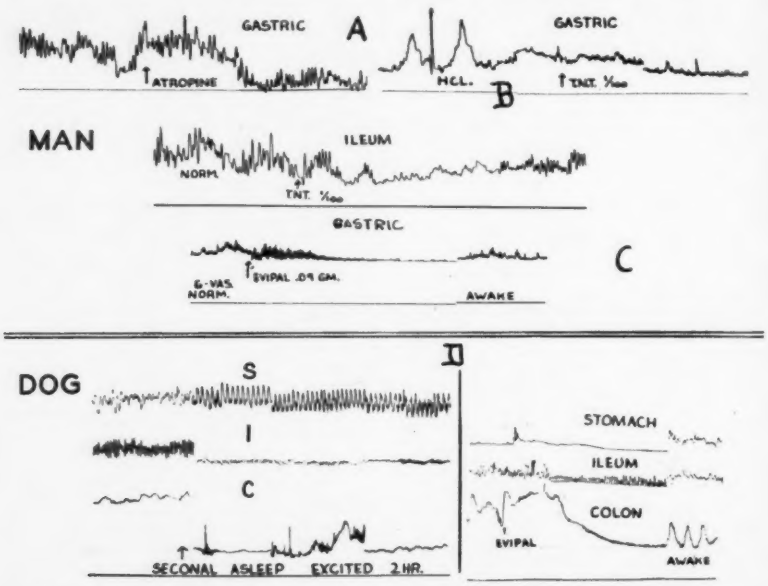


CHART 3.—(A) Action of atropine (0.65 mg.) upon the fasting human stomach. Note relaxation and some reduction in amplitude of contractions. (B) Action of nitroglycerine (0.65 mg.) upon the human fasting stomach and ileum. Note reduction of both tone and amplitude of contractions. (C) Evipal (0.9 Gm.) intravenously. Note relaxation and total inhibition of the stomach during anesthesia and prompt return of tone and activity upon regain of consciousness. (D) Action of seconal and of evipal upon the stomach, ileum and colon of the dog. Note inhibitory actions with both drugs but prompt restoration of normal tone and motility with return of consciousness after evipal, but continued inhibition two hours after administration of seconal.

tract with normal frequency, there was great reduction of amplitude. The inhibition persisted throughout the period of observation, three hours.

(4) Evipal intravenously (Chart 3).

(a) Man—0.9 Gm.

In two subjects, the stomach developed an immediate reduction of tone and, with complete loss of consciousness, total abolition of motor activity. Normal tone and activity returned promptly as complete consciousness was regained (after approximately 30 minutes).

(b) Dog—0.8 Gm.

In two dogs, there developed, immediately with loss of consciousness, a marked reduction of tone in the stomach, ileum and colon. Muscular activity of the stomach and colon was entirely abolished. In the ileum rhythmic contractions continued with diminished amplitude, but peristalsis was abolished.

Immediately following the return of consciousness, both tone and muscular activity became normal in all three segments of the gastro-intestinal tract.

III. Combined Effects (Charts 1 and 5).

(1) Morphine and Atropine.

As has been demonstrated by Magnus, Plant and Miller, Orr and Carlson and Veach, morphine and atropine administered together, in therapeutic doses, counteract each other so that the motor effect of morphine and the inhibitory effect of atropine upon the gastro-intestinal tract are counteracted, and relatively little effect results.

This fact was confirmed by the following observations in one man and in two dogs.

(a) Man. In a patient who was showing vigorous peristaltic contractions of the stomach and ileum following the administration of dilute hydro-

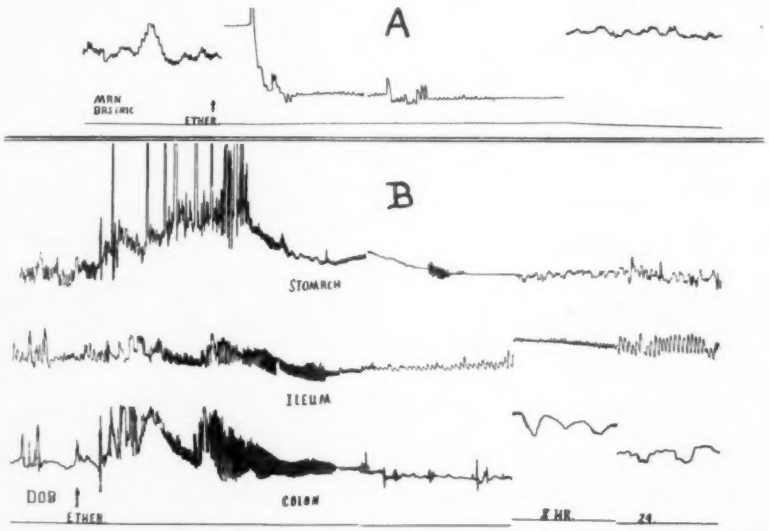


CHART 4.—(A) Action of ether upon the stomach of a man and (B) upon the stomach, ileum and colon of the dog, as registered simultaneously. Note strong inhibitory and relaxing action during surgical anesthesia and restoration of fairly normal function in stomach and colon eight hours, and of ileum 24 hours later.

chloric acid, atropine (0.65 mg.) caused prompt abolition of activity and diminution of tone. Morphine, 16 mg., was then given and caused a prompt restoration of normal tone and activity.

(b) Dog. Following the retching and vomiting after the administration of 16 mg. of morphine in two dogs, there was a sharp rise in the tone of both ileum and colon and a slight increase in gastric tone. In all three organs there was no change in frequency but a marked decrease in the amplitude of contractions. Atropine, 0.65 mg., given at the height of the morphine action caused the amplitude of contractions of the stomach and ileum to increase and that of the colon to decrease in one dog and had no effect in one. In the latter the tone of the bowel was diminished and that of the stomach increased.

IV. Anesthetic Agents.

(1) Ether (Chart 4).

(a) Man. The effects of ether anesthesia upon the stomach were observed in two patients and upon the ileum in one. In all three cases minor operations remote to the abdomen were carried out; namely, manipulation of a fracture in one case and vaginal plastic repairs in two. During surgical anesthesia there was a marked reduction of tone, and peristalsis was completely abolished. In the ileum, rhythmic contractions continued with diminution in both frequency and amplitude. With return of consciousness the tone and activity became reestablished slowly. At the end of 24 hours the con-

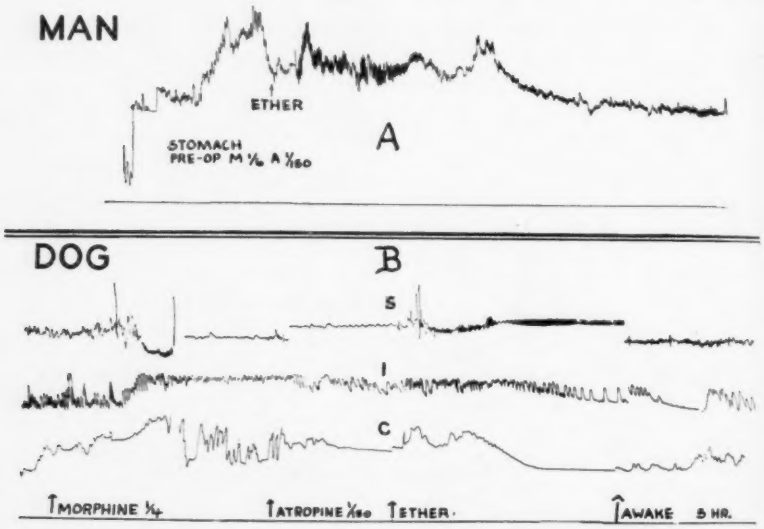


CHART 5.—(A) Action of ether upon the stomach of a man and (B) upon the stomach, ileum and colon of the dog, registered simultaneously. In both instances these had been administered preanesthesia medication of morphine (¼ gr.) and atropine (1/150 gr.). Note that this premedication lessened the inhibiting action of ether.

tractions of the stomach were still smaller than normal. The ileum, within one hour after return of consciousness, had developed an abnormally increased degree of muscular activity.

(b) Dog. Observations were made in two dogs. With induction of anesthesia there was an excitement stage characterized by rapid irregular oscillations of great amplitude and an increase in tone of both stomach and bowel. This resulted presumably from "breath-holding," vigorous contractions of the abdominal muscles and from the accompanying cyanosis. With the onset of and during surgical anesthesia there was a marked reduction of tone and cessation of motor activity except in the ileum where both rhythmic and peristaltic contractions were retained but were relatively feeble. Both tone and motor activity were slowly reestablished with return of consciousness. The colon and ileum promptly developed abnormally increased tone which was still evident 24 hours after return of consciousness. Twelve hours elapsed before the stomach had reestablished normal activity completely.

(2) Ether with Preliminary Medication of Morphine and Atropine (Chart 5).

(a) Man. Premedication, morphine 16 mg., atropine 0.43 mg. Records were made of the stomach in two patients, during exploration of a retroperitoneal tumor in one and during appendicectomy in one. Following the irregularly increased tone and muscular activity during the excitement stage, the tone gradually lessened but throughout remained elevated above the preanesthetic level. Muscular activity was much diminished but never entirely abolished. In comparison with ether anesthesia alone the premedication lessened the inhibitory effect of ether.

(b) Dog. Premedication, morphine 16 mg., atropine 0.43 mg. Observations were made in two dogs. The effect of ether anesthesia as observed in the previous experiments became definitely altered by premedication; that is, in respect to its effect upon stomach and ileum. These organs showed no loss of tone and continued to contract feebly. The colon, however, relaxed and ceased to contract as it did under the influence of ether alone. In both stomach and bowel premedication definitely delayed the return of normal activity.

(3) Nitrous Oxide and Oxygen (Chart 6).

(a) Man. The effects of nitrous oxide-oxygen anesthesia upon the stomach were studied in two cases. There occurred immediately and throughout the period of anesthesia greatly and very irregularly increased contractions. They were increased both in respect to frequency and amplitude. Tone was moderately increased. Immediately upon discontinuing the anesthesia there followed complete inhibition of motor activity and this persisted for approximately one hour. Gastric tone, however, remained slightly elevated. Motor function was reestablished slowly and was still subnormal three hours after anesthesia had been discontinued.

(b) Dog. Records were made of two dogs. The stomach, ileum and colon reacted during anesthesia precisely as did the stomach of man as described above. However, after the administration of nitrous oxide had been stopped, the stomach continued to contract rapidly and violently and this was concomitant with retching. Activity in the ileum and colon was almost completely abolished and the tone diminished for 30 minutes. Normal function was reestablished in the stomach and ileum in one hour and in the colon in approximately two hours. A record made eight hours after anesthesia showed increased activity in all three organs.

The above interpretations of the records of nitrous oxide anesthesia in both man and dog are misleading. Undoubtedly the changes interpreted as increased tone and activity represented the pressure factors exerted upon the stomach and bowel by the rigidity of the abdominal muscles and by deep breathing.

(4) Nitrous Oxide-Oxygen and Ether (Chart 6).

(b) Dog. In two dogs, these combined anesthetic agents produced a curious effect. The stomach responded precisely as it did to nitrous oxide-

oxygen alone in the preceding experiment. During anesthesia there was increased tone and motor activity, followed, after the return of consciousness, by decreased tone and almost total inhibition which lasted longer than two hours. The ileum and colon reacted precisely as they did to ether anesthesia alone in a preceding experiment. Tone was greatly reduced and muscular activity almost completely abolished during anesthesia but promptly became reestablished and assumed slightly exaggerated activity after consciousness was regained.

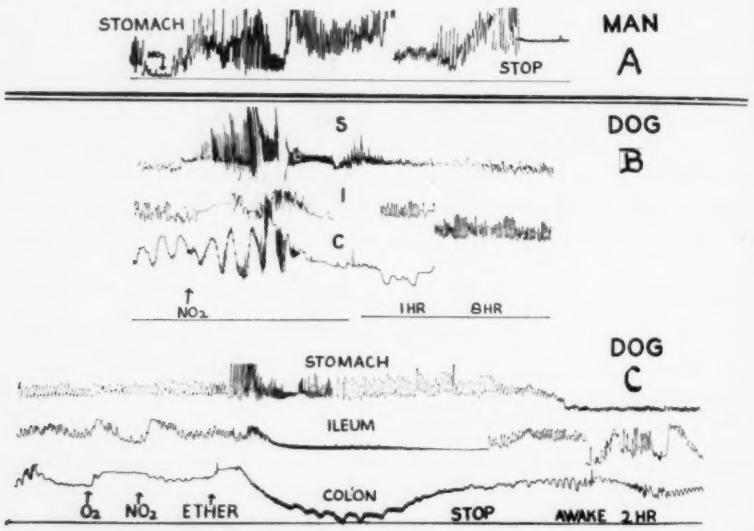


CHART 6.—(A) During nitrous oxide anesthesia the stomach of a man and (B) the stomach, ileum and colon of the dog show a primary increase of tone with irregular excursions which probably result from transmission of rapid, deep respiratory excursions and the muscular rigidity associated with cyanosis. (C) Combined nitrous oxide and ether anesthesia in a dog showing inhibitory influence of ether upon the ileum and colon, and the motor influence of nitrous oxide upon the stomach during anesthesia and its inhibitory influence upon this viscus after anesthesia was discontinued and consciousness was regained.

Note almost total inhibition in all organs following withdrawal of nitrous oxide and recovery from anesthesia, and that the inhibition lasted for approximately one hour, and tone and motor activity were normal at eight hours.

(5) Spinal-Novocain. No premedication (Chart 7).

(a) Man. Novocain, 150 mg. with ephedrine subcutaneously. Observations of the ileum and stomach were made in two patients while undergoing simple appendicectomies.

The stomach showed a slight reduction of tone and greatly diminished muscular activity during anesthesia. With return of sensation there developed normal tone and motor hyperactivity. Contractions were exaggerated both in frequency and amplitude. This state of hyperactivity persisted for at least 72 hours after operation as shown by recordings at 24, 48, and 72 hours.

The ileum developed increased tone with a slight reduction of all motor activity during anesthesia. The tone receded with return of sensation and remained relatively normal. Rhythmic contractions showed increased amplitude, and peristalsis a diminution of both frequency and amplitude.

(b) Dog. Novocain, 100 mg.

The influence of spinal anesthesia upon the stomach, ileum and colon was observed in two dogs. The effect upon the stomach was slightly inhibitory. Both tone and motor activity were slightly diminished. The action upon the bowel was motor. In the ileum of both dogs and the colon of one the tone and motor activity were increased. The colon of the other dog showed little or no change.

In all three portions of the gastro-intestinal tract the tone and motor activity promptly reverted to normal as anesthesia dissipated, and for three hours postanesthesia there was no appreciable change.

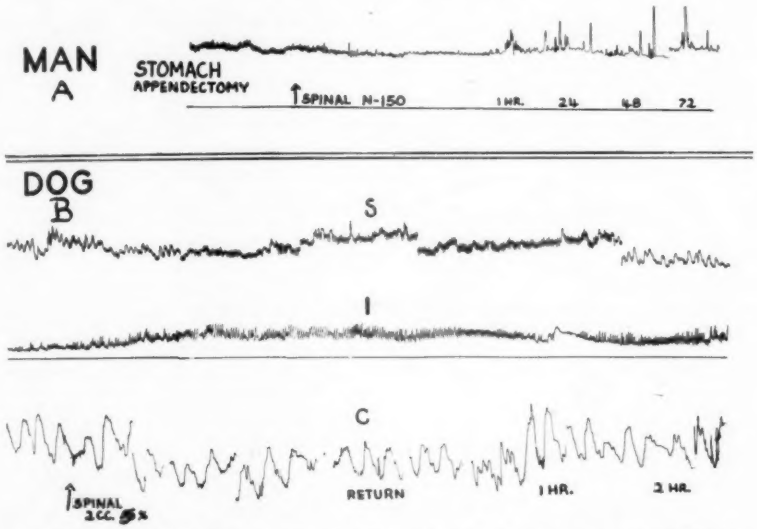


CHART 7.—(A) Tracing of changes within the stomach of a man undergoing appendicectomy under spinal anesthesia which reached to the level of the sixth dorsal spinal segment. Note a reduction of amplitude of contractions but no change in tone during anesthesia, and an increase in frequency and amplitude of contractions immediately following dissipation of anesthesia and at observations made 24, 48, and 72 hours later. (B) Spinal anesthesia in a dog with level of anesthesia up to the fifth dorsal segment. Note increase in tone and muscular activity of both stomach and ileum and no change in the colon; also restoration of normal tone and peristaltic activity with elimination of anesthesia and continued normal function at observations one and two hours later.

(6) Cyclopropane (Chart 8).

(a) Man. Records of the influence of cyclopropane upon the stomach were obtained in four patients, one after premedication of morphine and atropine. Two were given anesthesia without operation solely for purposes of this study. In one case, a biopsy of a cervical tumor was performed and in one a fractured forearm was manipulated. In all cases there was an increase in tone and in rhythmic contractions but inhibition of peristalsis during the stage of surgical anesthesia. Immediately upon return of consciousness there was a diminution of tone to a subnormal level and a return of normal motor activity which continued during observation periods as long as three hours.

(b) Dog. Observations in two dogs showed increased tone and activity

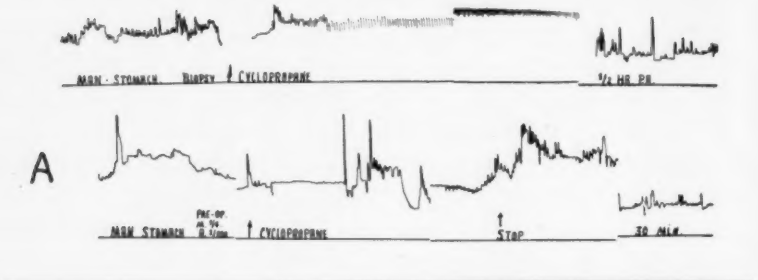
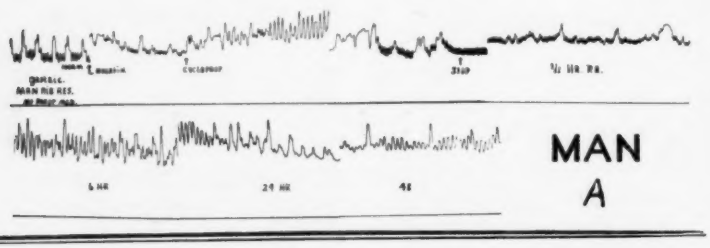


CHART 8.—(A) Action of cyclopropane anesthesia upon the human stomach, first cyclopropane alone and secondly cyclopropane following premedication of morphine and atropine. Note that gastric tone was increased with some inhibition of contractions and that the premedication caused cyclopropane to have less stimulating effect. (B) In the dog, cyclopropane increased both tone and motor activity of the stomach, increased tone of the ileum and was temporarily inhibitory to the colon. Upon a return of consciousness normal activity and tone were immediately reestablished.



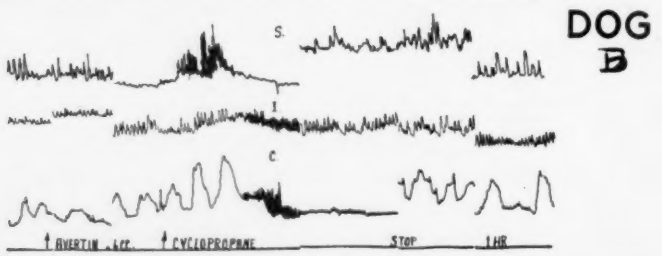


CHART 9.—(A) A study of the stomach of a man made during a Schede thoracoplasty for chronic empyema under combined avertin-cyclopropane anesthesia. Note an increase of tone with fairly normal peristaltic activity throughout period of anesthesia and restoration of normal tone and motor activity immediately following return of consciousness and hyperactivity at observations made six, 24, and 48 hours later. (B) Combined avertin-cyclopropane anesthesia in the dog caused no significant change in the stomach and ileum but was inhibitory to the colon. Normal activity in all three segments of the gastro-intestinal tract returned immediately after the anesthetic was stopped and consciousness was regained.

in the stomach, increased tone and diminished activity in the ileum and decreased tone and activity in the colon during surgical anesthesia. Immediately after anesthesia was stopped the colon reestablished and retained during an observation period of six hours normal tone and activity. Aside from brief periods of abnormal activity immediately upon regaining consciousness, the stomach and ileum did likewise.

(7) Cyclopropane Supplementary to a Basal Anesthesia of Avertin (Chart 9).

(a) Man. Satisfactory gastric readings were obtained in only one patient. In this patient a Schede's thoracoplasty for empyema was performed. Promptly following the rectal administration of avertin (80 mg. per kg. of body weight) there developed some diminution of motor activity. With the addition of cyclopropane, gastric tone and activity were temporarily increased, but with the establishment of complete surgical anesthesia the tone and activity became relatively normal. Observations made six, 24, and 48 hours after recovery from anesthesia showed a moderate degree of hyperactivity.

(b) Dog. Two dogs were given 0.6 cc. of avertin rectally and records made of the stomach, ileum and colon. No appreciable effect was produced. As cyclopropane was supplemented there was a brief excitement period with an increase in tone of all three segments and this was followed during surgical anesthesia by relaxation and total abolition of motor activity of the colon and by an increase in tone and motor activity of the stomach and ileum. All three segments promptly reestablished normal tone and activity with return of consciousness.

(8) Avertin, 100 mg. per Kg. of body weight (Chart 10).

(b) Dog. Two dogs were given avertin, 0.6 cc. per rectum, and observed for a period of four hours. Except for a slight decrease in tone of the ileum and colon during the period of light anesthesia, and subsequently, a moderate increase in motor activity of the stomach and ileum, no definite effect was produced.

V. Oxygen and Carbon Dioxide Saturation (Chart 10).

(1) Oxygen. In two dogs the inhalation of pure oxygen caused an increase in tone and an increase in the frequency of contractions of the stomach, ileum and colon but a decrease in amplitude of the contractions. Normality was promptly reestablished when administration of oxygen was discontinued.

(2) Carbon Dioxide.

After a brief recovery period from oxygen administration, carbon dioxide was administered to the same animals. In both stomach and bowel there developed a reduction of tone and irregularly increased motor activity (difficult to evaluate from effect resulting from rapid, deep breathing). Immediately after removal of the mask, there was a further loss of tone in all segments and almost complete inhibition of motor activity of the ileum and colon for approximately one hour. The purpose and significance of this group of studies are dealt with in the discussion.

DISCUSSION.—The drugs which were studied are representative of those commonly employed in the immediate pre- and postoperative care of patients. It has been shown that they have pronounced effects upon the tone and muscular activity of the gastro-intestinal tract. The effects of any one of them were either predominantly motor or inhibitory. However, seconal (representative of barbiturates) in therapeutic doses had mixed actions. It was motor to the stomach and inhibitory to the intestine. Also the degree with which the drugs which were studied influenced the tone and activity of the various

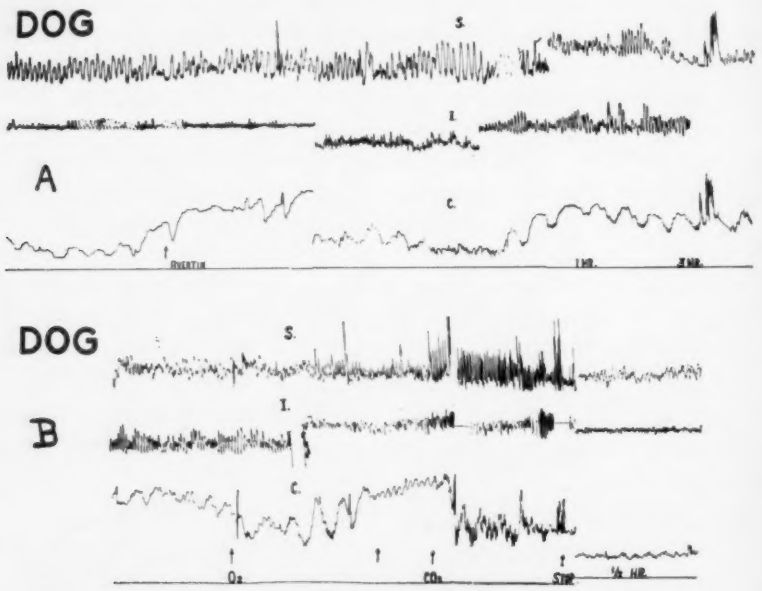


CHART 10.—(A) Simultaneous tracings of the influence of avertin upon the stomach, small intestine and colon of a dog. Note a slight motor effect upon the stomach and a slight inhibitory effect upon the colon and hyperactivity of all three organs one and three hours later. (B) Simultaneous tracings of the influence of oxygen and carbon dioxide upon the stomach, ileum and colon of a dog. In all three organs oxygen had a motor effect and carbon dioxide an inhibitory effect, the latter became more apparent after inhalations of carbon dioxide were discontinued. The inhibitory effect lasted for approximately one hour.

portions of the gastro-intestinal tract varied. As a rule the colon showed the most profound influence and the ileum the least.

In general, these experimental results are simply confirmatory of those previously reported by Schapiro, Orr, Plant and Miller, Gruber, and Robinson, Veach, Olmstedt, and Beans.

As in the case of the drugs discussed above, the anesthetic agents which were studied were either predominantly motor or inhibitory in their effects upon the gastro-intestinal tract. If tone, with or without increased activity, is used as a criterion of action, avertin, cyclopropane and spinal (novocain) anesthetics were provocative of motor responses. Ether, nitrous oxide and evipal caused relaxation of the gastro-intestinal tract with partial or complete abolition of contraction. Their actions, therefore, were unmistakably inhibitory. The true inhibitory effect of nitrous oxide became apparent only after

the anesthesia become sufficiently deep to cause some relaxation or after it was discontinued. The rigidity of the abdominal muscles, the deep breathing and the cyanosis which this anesthetic produced caused the illusion of an increase in tone and activity.

The premedication of morphine and atropine lessened the depressing effect of these inhibitory anesthetic agents.

Thus, if the reader will refer to the analysis of the clinical cases tabulated in Table I, it becomes apparent that the symptoms of disturbed gastro-intestinal function occurred with much greater frequency and severity in the group of cases which were anesthetized with the depressing and inhibiting types of anesthetic agents, namely, ether and nitrous oxide, alone or in combination.

The studies of the gastro-intestinal tone and activity in both man and dog showed also that the postanesthetic reestablishment of normal tone and activity occurred more slowly in the group given inhibitory anesthetics. A period of hyperactivity developed eventually, following all anesthetics.

Curtis and his associates have shown that from 24 to 72 hours following anesthesia and celiotomy, gastric hypermotility develops and persists from two to three weeks. During the first week, the periods of increased motility were associated with epigastric distress, interpreted by the patients as gas-pains, and subsequently associated with sensations interpreted as hunger.

Why should drugs which produce anesthesia have widely different effects upon the motor activity of the gastro-intestinal tract? There is apparently no relation of such effects to their actions upon the central nervous system. Miller has shown that the effects of ether, chloroform, nitrous oxide and ethylene upon a loop of small bowel after denervation were essentially the same as they were while its nerve supply was intact.

In certain nonabdominal nonsurgical diseases there occur nausea and vomiting, distention and occasionally gas-pains. These diseases are associated with toxemia, such as occurs in pneumonia or with abnormality of either fluid or oxygen balance, such as occurs with general tissue hydration in certain cases of nephritis and with cyanosis in congenital heart disease.

With the suggestion from Dr. Roy McClure that tissue anoxia might be a factor of inhibitory influence to the musculature of the stomach and bowel, studies with oxygen and carbon dioxide saturation were carried out. In each instance the inhalation of pure oxygen caused in dogs an increase in gastro-intestinal tone, and the inhalation of pure carbon dioxide caused lessening of tone and, in the bowel, almost complete inhibition of motor activity for a period of approximately one hour.

CONCLUSIONS

(1) Drugs commonly employed in the pre- and postoperative care of patients have either strong motor or strong inhibitory influences upon the tone and peristaltic activity of the gastro-intestinal tract.

(2) Anesthetic agents are in part responsible for some of the late as

well as the immediate postoperative symptoms of nausea and vomiting, distention and gas-pains.

(3) The different types of anesthetics vary greatly in respect to the frequency, the degree and the duration of associated symptoms of disturbed gastric and intestinal function. Likewise, anesthetics vary greatly in their respective actions upon the gastro-intestinal tract. Cyclopropane-avertin, spinal and cyclopropane (alone) have predominantly stimulating or motor actions. Ether and nitrous oxide, either alone or in combination, have depressing or inhibiting effects upon gastric and intestinal tone and peristalsis. There is a close correlation between the degree with which gastric and intestinal motor activity is diverted from normal toward inhibition during anesthesia and the frequency, duration and severity of postoperative symptoms of gastro-intestinal dysfunction.

(4) It is suggested that the influence an individual anesthetic has upon the gastro-intestinal tract may be dependent upon its influence upon the relative quantity of oxygen in the blood or tissues during anesthesia. When inhaled, oxygen stimulates and carbon dioxide inhibits gastro-intestinal motor activity.

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DISCUSSION.—DR. GEORGE M. CURTIS (Columbus, Ohio): During the past five years a group of us, and particularly Louis Barron, Harry Veach, and Frank Hamilton, have become interested in this problem of gastro-intestinal tone and motor activity. Moreover, with the cooperation of a number of willing patients, we have determined the motility of the human stomach under a variety of clinical conditions, both pre- and postoperatively, as well as in certain instances under the influence of spinal anesthesia. We have observed the after-effects of operative measures under general anesthesia, although no studies have been made during such procedures.

As a consequence, we are greatly interested in this presentation, and particularly in Doctor Bisgard's excellent experimental work, in which he has demonstrated the simultaneous activity of the stomach, small and large intestines; also the effects of certain drugs as well as anesthetic agents.

Patients as a rule are not particularly averse to this procedure, and, ordinarily, cooperate well when it is explained to them. In fact, they often become interested in the graph as it develops on the kymograph. Moreover, the process of swallowing the balloon, which is deflated and enclosed in a capsule, and the subsequent intubation have their counterparts in the ordinary use of suction drainage and fractional gastric analysis.

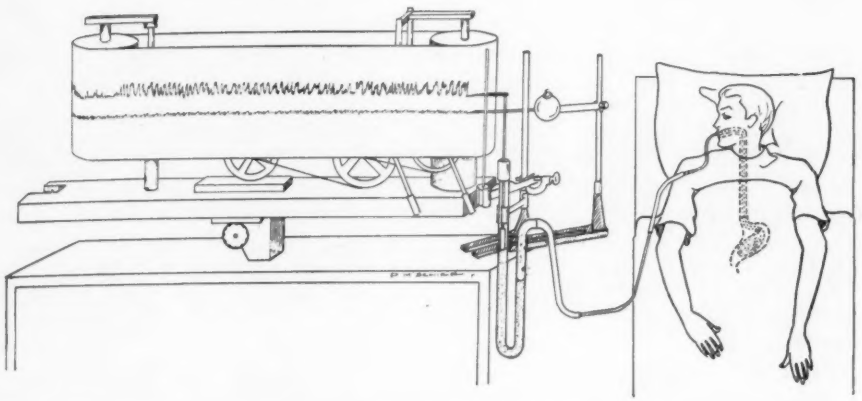

FIG. 1.—The apparatus used to investigate gastric motility at the bedside (Arch. Surg., **32**, 577, 1936). The ink-writer is described elsewhere (Jour. Pharm. and Exper. Therap., **61**, 230, 1937).

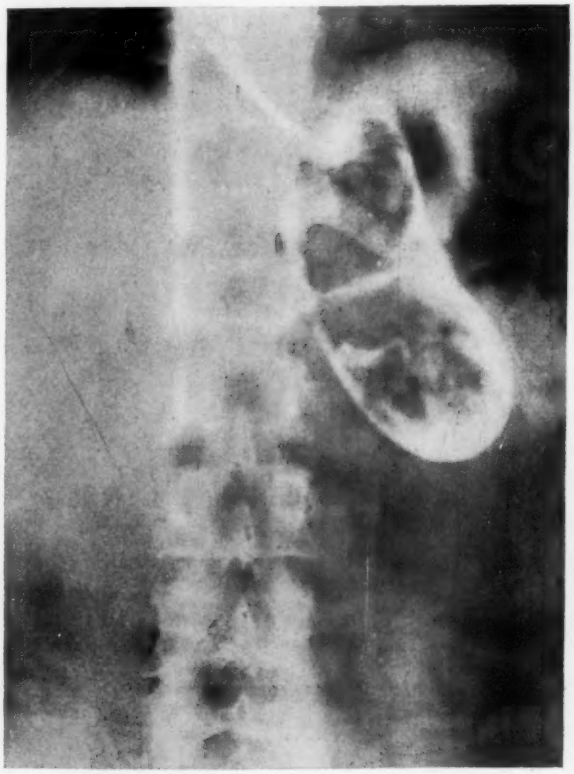

FIG. 2.—The balloon in place in the stomach during gastric motility studies (Arch. Surg., **32**, 577, 1936).

Since the details of our extensive studies are largely a matter of record, I will allude but briefly to certain of our findings.

Figure 1 shows the apparatus which was used in making these studies. It is essentially that which Carlson used in his extensive investigations. We have added, however, one important feature. In our original studies we used the usual smoked drum, and found that the bed linen, the white interns' suits, and the nurses' uniforms were sometimes smudged by the soot. Consequently, I asked one of my residents if he would devise an ink-writer for the white paper. He was unable to do so. Later, however, there came to us, as one of our residents, a student from Starling's laboratory. Within a week, he had devised a simple ink-writer, which we now use and which makes the work in the hospital much easier.

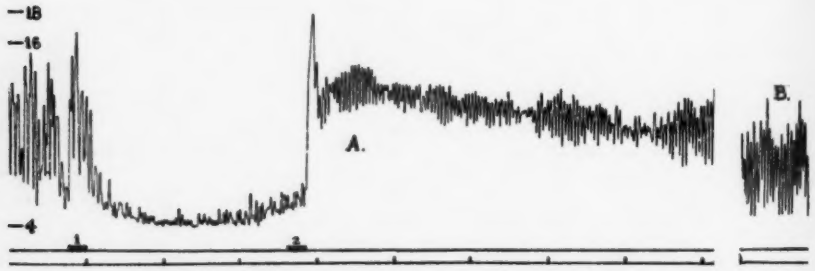

FIG. 3.—The inhibitory effect of atropine (0.6 mg. intravenously) upon the motor activity of the human stomach is shown at (1) The reversal of this effect to motility by morphine (15 mg. intravenously) is shown at (2) and by (A). At (B) is shown the resultant motility after 98 minutes from (2) (Jour. Pharm. and Exper. Therap., **61**, 230, 1937).

Figure 2 is a roentgenogram showing the position of the balloon in the stomach. In that way it can be controlled and the tube length kept constant.

Figure 3 presents a graph showing the reversal of the morphine motor effect, as was brought out by Doctor Bisgard. Morphine was first given with an ensuing increased motility, followed by atropine given at this point with a subsequent inhibition.

From an extensive experience with this procedure we would conclude that it is readily applicable in the hospital and that it has definite clinical value in recognizing disturbances of gastro-intestinal motility and their control.

DR. ALFRED BROWN (Omaha, Neb.): This excellent demonstration by Doctor Bisgard determines two points: First, gastric investigation began with the classic experiments of Beaumont made upon Alexis St. Martin. This was a case of surgical trauma and in all subsequent experiments there has been an element of doubt as to whether the results were accurate because of the trauma inflicted upon the intestine during the experiment which required the introduction of an instrument through a wound in the gut. Consequently there remained the question whether, after injury, the intestinal tract regained sufficient normality to make the readings accurate. The method of the indwelling balloon obviates the necessity for surgical trauma and we can conclude that the results by this method are accurate, because the similarity between the results on man, as shown by Doctor Bisgard, upon whom no intestinal surgery was performed, and the results in dogs, in whom the various types of intestinal pouches were made, seems to go far toward demonstrating that following surgery upon the intestine, the tract tends to restore itself to normal action.

Second, these experiments demonstrate the reasons for postoperative intestinal distention in the ether-nitrous oxide group and the lessened amount

of similar distention following the administration of cyclopropane or spinal anesthesia, which has long been recognized clinically. The ether-nitrous oxide group paralyzes the intestinal muscles. As sympathetic nerve control returns, there is a resultant incoordinated action of intestinal musculature. This gives rise to irregular spasm and abnormal peristalsis causing the so-called gas-pains. Cyclopropane and spinal anesthesia act apparently on the sympathetic nervous system and there is at no time a paralysis of intestinal musculature. Consequently, postoperative return of normal peristalsis is brought about by a harmonization between the sympathetic and parasympathetic nervous systems which had temporarily been disturbed during the period of anesthesia.

The same effect is noted in paravertebral anesthesia, in which the sympathetic fibers connecting the ganglia with the somatic nerves are paralyzed. Doctor Bisgard showed a slide of a thyrotoxic patient in whom the administration of hydrochloric acid and pepsin changed an almost tonic contraction of stomach wall to normal rhythmic contraction. This same result has been noted in my cases of hyperthyroidism which have been given hydrochloric acid and pepsin during their preparation for operation. In 1930, I called attention to the diminution or absence of free hydrochloric acid in hyperthyroidism. Since that time this observation that diminished or absent free hydrochloric acid is a constant finding in hyperthyroidism has been determined in many other cases. The tonic contraction of the stomach brought about by stimulation of the sympathetic system by the hyperthyroidism accompanied by the lack of free hydrochloric acid, explains the increased appetite and accompanying loss of weight in these cases.

In some of my cases, stomach readings have also been made at the time of operation. No hydrochloric acid-pepsin was given preoperatively. The contractions of the stomach at the beginning of the operation were almost tonic, as shown in Doctor Bisgard's chart. With the administration of paravertebral anesthesia, in which the superior cervical sympathetic ganglion and nerves are temporarily paralyzed, gastric contractions changed from the tonic type to a normal peristaltic wave a few minutes after the anesthetic took effect and continued for the duration of the anesthesia.

These results raised the question as to whether the influence of anesthesia upon the sympathetic system does not also have a bearing upon postanesthetic intestinal physiology in addition to the anoxemia which Doctor Bisgard has described.

Dr. Roy D. McClure (Detroit): Doctor Bisgard mentioned the studies which we are making at the Henry Ford Hospital concerning these drugs and their relation to anoxia. He asks the question as to whether our work might show that these drugs did produce an anoxia which helps to explain his results. We have, for quite a time, been working on the question of anoxemia, and Doctor Hartman is reporting the results of that work in this afternoon's session. Unfortunately, in anesthesia as practiced to-day, we seldom have straight inhalation anesthetics, with ether, nitrous oxide or ethylene gas. In most patients, preoperative sedative drugs are given, and we have shown, definitely, that the amount of oxygen in the blood is diminished after many of these sedatives, as given in fairly large doses. In some instances there are dire results; in other cases, results which are more or less imperceptible by our present methods of examination. We do have evidence to show that there are varying grades of damage with resulting permanent changes in the central nervous system due to anoxia, the grade of damage being dependent upon the amount of sedatives and anesthetics. (See Anoxia: A Source of Possible

Complications in Surgical Analgesia and Anesthesia, by R. D. McClure, F. W. Hartman, J. G. Schnedorf, and V. Schelling. ANNALS OF SURGERY, **110,** 835, November, 1939.)

DR. PETER HEINBECKER (St. Louis): I would like to ask Doctor Bisgard how many of these effects on the intestinal tract does he consider to be local effects, and to what extent does he consider them to be the end-result of an effect on the central nervous system? I think that there is little evidence to indicate that under ordinary states of anesthesia the responses to direct stimulation of peripheral or sympathetic nerve structures are affected in a paralytic way. Under ordinary states of anesthesia direct stimulation of peripheral somatic and sympathetic nerve structures yields relatively normal responses.

DR. LEO ELOESSER (San Francisco): I should like to supplement Doctor Heinbecker's question by another. I wonder whether Doctor Bisgard has made similar experiments under anesthesia during operations on the extremities? The fact that most of his operations were celiotomies has possibly added an additional complicating factor to the evaluation of the effect of drugs on the gastro-intestinal tract. If these studies were made upon patients with intact, normal abdomens, this complication might be eliminated.

DR. J. DEWEY BISGARD (closing): In answer to Doctor Heinbecker's question, Plant and Miller, at the University of Iowa, made some observations, similar to mine, of the effect of ether, chloroform and nitrous oxide, after removing the nerve supply to the isolated loop of small bowel, and they got the same responses with and without the nerve supply, so they felt that the action of these anesthetic agents was peripheral, and independent of the nervous system.

In answer to Doctor Eloesser's question, several of these patients, some of those that I showed you a few minutes ago, were minor operations such as biopsies remote to the abdomen, and we got the same responses there.

THE ASSAY OF GENERAL ANESTHETIC AGENTS*

HENRY K. BEECHER, M.D.

BOSTON, MASS.

FROM THE SURGICAL LABORATORIES OF THE HARVARD MEDICAL SCHOOL AT THE MASSACHUSETTS GENERAL HOSPITAL BOSTON, MASS.

PROPRIETARY anesthetic agents are appearing on the market at an increasingly rapid rate. The advocacy of first one and then another of these changes so rapidly in various institutions, a yardstick of unchanging criteria must be at hand if new agents are to be evaluated accurately and safely. If the good are to be recognized and employed and the bad discarded, a number of factors must be taken into account.

Perhaps the greatest obstacle to success in estimating the merits of anesthetic agents is our ignorance of the mechanism of anesthesia. The anesthetist confronted by the anesthesia process stands in much the same position as the internist faced with a disease of unknown etiology—his treatment must be symptomatic, empiric. The only basis we have for evaluating anesthetic agents is an empiric one. Such a method can be as logical, and successful, as the symptomatic treatment of disease often is. Just as precision and success in the treatment of disease usually considerably increase once the etiology is known, so with anesthesia: When the mechanism of the process is better understood it will undoubtedly be possible to evaluate agents with more skill than we now can. Until such progress has been made we must continue to depend upon empiric findings for our estimations.

Certainly all anesthetic agents fall short of the ideal, though some of the individual qualities of each may be nearly what we could wish. If the quality of one's evaluation is to be unchanging, each agent must be pitted against the ideal, and the present discussion will be concerned with the qualities of the ideal anesthetic agent.

PHYSICAL AND CHEMICAL QUALITIES OF THE IDEAL ANESTHETIC AGENT

I. *Potency, Narcotic Strength:* The most formidable enemy the anesthetist must combat is anoxia, for as Haldane has put it, anoxia "not only stops the machine but wrecks the machinery." With any agent it should be possible to use at least 15 per cent oxygen. That is to say, *the narcotic strength of an anesthetic agent should be great enough so that the partial pressure† of it in the air breathed need not exceed about 650 Mm. Hg.*

The partial pressure‡ required for full surgical anesthesia under several

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

† The concentration of an agent necessary to produce a given level of anesthesia by inhalation may be expressed in terms of grams of anesthetic per liter of inhaled gas mixture. The anesthetic vapor or gas should not, even for deep anesthesia, occupy more than 85 per cent of the liter. Expressing it another way, it should not exert more than $0.85 \times 760 = 646$ Mm. Hg partial pressure.

‡ Dry gas or vapor at a temperature of 37° C. and 760 Mm. Hg pressure.

common anesthetic agents, and the oxygen percentages permitted are detailed in Table I.

TABLE I

	Partial Pressure (Mm. Hg)	Oxygen Percentage
Chloroform	5	99.3
Ether	25	96.7
Ethyl chloride	35	95.4
Cyclopropane	150	80.0
Ethylene	680	10.0
Nitrous oxide	975	*

Above the line, none of the partial pressures is too high, and an excess of oxygen is possible with any of these agents.

II. *Solubility:* When equilibrium of a gas has been established between the alveolar air and the blood, the ratio of the quantity dissolved in, say, one liter of blood to that in one liter of air is called the solubility coefficient of the gas. The solubility of an anesthetic agent in the blood must be low enough so that a relatively high partial pressure can be worked with (but not so high that the oxygen will be dangerously low), for *with a high partial pressure and a low solubility, rapid induction and rapid recovery from the anesthesia are possible.* If this test be applied to the common inhalation anesthetic agents (Table II).

TABLE II

	Partial Pressure 37° C. 760 Mm. Full Anesthesia	Solubility Coefficient
Chloroform	5	10
Ether	25	14
Ethyl chloride	35	2.5
Cyclopropane	150	0.49
Ethylene	680	0.74
Nitrous oxide	975	0.47

it is evident that it is successful. All those below the line have the characteristic of a rapid induction and a rapid recovery period, while those above are, by comparison, slow.

* At normal atmospheric pressure it is not possible to obtain true, deep anesthesia with nitrous oxide, even if *all* oxygen is cut out. In actual practice the patient may be depressed by means of preanesthetic medication, by basal anesthesia, and so on, to such an extent that the additive effect of nitrous oxide with 10 per cent oxygen will produce anesthesia adequate for the task at hand. Even so, in occasional cases, this is not possible without accompanying anoxia and cyanosis. Some bold individuals go so far as to use the effects of anoxia deliberately in their efforts to depress patients under nitrous oxide. Such a practice is indefensible.

III. *The Hazard of Explosion:* One of the great needs of surgery at the present time is an inhalation anesthetic agent that will neither burn nor explode; so that it may be employed safely in the presence of the cautery. Of the six agents we have been considering in this discussion, two will neither burn nor explode: nitrous oxide and chloroform; and yet neither of these is satisfactory, for example, for thoracic surgery nor for surgery in the mouth. Here the oxygen supply is at a premium. When the aerating power of the body is crippled, the oxygen percentage permissible with nitrous oxide is inadequate, even though only light anesthesia may be necessary. In the case of chloroform, cardiac depression of too great a degree to be allowable occurs, for these cases will be under a severe circulatory strain as a consequence of the operation, and the use of an anesthetic agent which greatly cripples the heart is not sound. This depressant characteristic makes the use of chloroform hazardous even if one is willing to ignore the possibilities of ventricular fibrillation, or of late liver and kidney damage. Aside from its well known toxic effects, the use of chloroform is hardly desirable when the cautery must be used in the air-way, for a combustion product of chloroform is phosgene, one of the deadliest of the war gases. It is highly toxic to the lungs and well known to produce pulmonary edema in even extremely great dilution.

While it is often stated that the explosive nature of ether or cyclopropane or ethylene with oxygen is of comparable degree, data recently gathered tend to throw doubt on this. Possibly static electrical charges have a greater tendency to detonate ethylene-oxygen, or cyclopropane-oxygen mixtures than is true for ether-oxygen. However that may be, the fact remains, *with the ideal agent, explosive mixtures will not be formed with air or oxygen.*

Biologic Qualities of the Ideal Anesthetic Agent

I. *A Controllable Route of Administration Must Be Available:* At the present time, the most controllable route for the administration of general anesthetic agents is by inhalation. A recent trend makes the consideration of nonvolatile agents of importance. There are two main routes of administration of nonvolatile agents for general anesthesia—the veins or the rectum. Some agents, as avertin, can be introduced only through the rectum. But in the case of the barbiturates, many can be introduced directly into the blood stream. The recent recommendations of a half-dozen papers, that the barbiturates be introduced rectally, raise the question of the relative controllability of these two routes of administration.

Several points are pertinent to such a consideration:

(1) *Once an agent is placed in the rectum it is nearly impossible to recover any,* after it begins to exert its normal action or to give toxic effects. While high colonic enemas may be tried, in an endeavor to wash it out, the fact is, such action may sweep the offending agent higher in the bowel and allow even more rapid absorption with greater toxic effects to follow.

(2) Even though a solution of given volume may be injected into the rectum at a standard speed, *it is impossible to say to what height it will travel up the bowel.* There are a number of reasons for this. There is no need to point

out to a group of surgeons how uncertain cleansing of the bowel may be as a result of routine enemas. The height to which an anesthetic agent will rise on being placed in the rectum is determined in large part by the fecal content of the bowel. Other factors active in regulating height (and impossible of accurate evaluation) are tone of the bowel, peristalsis, and anatomic anomalies. Using a dilute barium solution under exactly the same conditions as avertin is used, Sebening[2] found on roentgenographic examination that in two patients the entire colon including the cecum was filled, in two the midascending colon was reached, while in four the hepatic flexure was attained and in four the midtransverse colon, in seven the splenic flexure and in one patient only the rectosigmoid junction was reached.

(3) It is well known that *the toxicity of the nonvolatile anesthetic agents depends to a great degree upon their rate of absorption.* With some of the agents, as with sodium barbital, while the blood level is rising as a result of absorption, it is counterbalanced by excretion through the kidney and a safe blood level may thus be maintained. In other cases, as with the fast acting barbiturate, evipal, a safe blood level depends in part upon liver destruction concomitant with absorption. An abnormally rapid rise in the absorption rate, however, easily upsets the balance experience has taught is safe, and serious toxic effects follow.

(4) The following statement, then, seems to be a reasonable one: If we cannot efficiently remove an agent once it is placed in the rectum, if we cannot control the height to which a solution injected into the bowel will rise, then it follows that we cannot control the rate of absorption. In other words, we cannot accurately control the toxicity of nonvolatile agents used rectally. If an agent can be used intravenously there is no reason to resort to the relatively inaccurate and unsafe rectal route. I wonder if the defenders of the rectal route of administration of the barbiturates are prepared to claim that there is any magic in the *route* of absorption: The implication is inescapable in some of the papers referred to, that rectal administration prolongs the action of the drug! The rate of administration can be precisely controlled through intravenous drip methods, and if toxic signs appear, the administration can be immediately curtailed. It seems evident that such a method is more desirable than one which cannot be precisely controlled.

II. *Factor of Safety; Toxicity:* The anesthesia process is by definition a reversible depression. It is a reversible approach toward death. This possibility of accident ought always to be remote. If any anesthetic agent allows irreversible change to occur, allows death to come near without adequate warnings far in advance and before irreversible change has occurred, it cannot be considered satisfactory. The well worn examples of ether and chloroform illustrate this. With ether over-dosage, the respiration fails and intake of the drug stops long before serious damage has occurred. Under chloroform, subtle and irreversible changes of fatal degree may occur in the liver and kidneys with no warning to the anesthetist. Or ventricular fibrillation may strike without warning. It is not yet possible to say whether or not such a

potentiality may greatly curtail the usefulness of cyclopropane; there is, however, worrisome evidence that this may be the case. To sum this up: *No side-toxicity other than that inherent in the anesthesia process itself should be present,* and easily detectable phenomena should warn of approaching danger long before the patient has suffered from the toxic effects of the drug used.

III. *Adequacy of Physiologic Effect:* Surgery of precision should be permitted without hurry or hindrance. In any such requirement, effects that are too widespread may also be a problem. With inhalation anesthesia the wasteful crippling of many of the organs of the body when anesthesia of only a limited region is desired, is unpleasant to contemplate. Observations of the last few years suggest that even inhalation anesthesia may increase in its specificity.

A great stumbling block to progress in knowledge of the anesthetic agents has been their multiple actions: There is the general action producing loss of consciousness, and specific actions attacking one system but not another. If we did not have proof that these dual effects could be turned to practical advantage, it would seem fanciful to suggest that such might be the case. But it is the case.

In the laboratory, we have learned that chloralose produces general anesthesia but spares the carotid sinus mechanism, that certain of the barbiturates spare the sympathetic nervous system. Clinically, we know that cyclopropane disturbs fewer organs than ether. If this agent is found in time to meet the requirements of usefulness and general safety outlined above, it must be accepted as a step forward. Extraordinary is the clinical finding that *sub*-general anesthesia doses of trichlorethylene will produce anesthesia of the fifth cranial nerve. A further requirement of the ideal anesthetic agent can be stated: *The normal activity of only a few organs shall be impaired.*

IV. *Elimination:* The ideal anesthetic agent will be one which is either rapidly destroyed or swiftly eliminated even in the presence of grave organic disease. One reason for the superiority of inhalation anesthetic agents over those of the nonvolatile group for general anesthesia lies in the ease of control of the volatile agents, and of most importance is the speed at which they can be eliminated if toxic effects appear. Progress in developing nonvolatile compounds that are rapidly eliminated through the kidneys or are rapidly destroyed by the liver, as in the case of the fast acting barbiturates evipal, pentothal, and others, raises the possibility that similar agents may be found, in time, to fulfill the requirement of controllability better than a gas or a vapor. Such is not yet the case. With the nonvolatile agents there is the further complicating factor that individual susceptibility varies widely. This has been illustrated many times both for barbiturates and for avertin.[1,3]

Statistical Requirements

The inescapable test to which most innovations in medicine must be subjected is whether or not they can lower the death rate for a given procedure.

Statisticians and their statistics are looked upon with considerable suspicion by the rest of the world. Statistics are not a substitute for common sense. On the other hand, some use of statistical methods is essential if common sense is to be preserved in the handling of data.

Anesthesia literature, perhaps more than that of any other division of medicine, is shot through with claims wholly unsupported by available evidence. No one can object if an individual wishes to report a few hundred anesthesias with no deaths. In certain cases, such reports are desirable, as, for example, when a new anesthetic agent is being tried and no one man has had opportunity to acquire a really adequate personal series. Strenuous objections can be raised and should be, if such reports contain any attempt to draw conclusions as to the safety or death rate or to make comparison with other agents of a similar or lower death rate.

Whether we like it or not, the fact remains that if anesthetic agent A has a death rate of 1:1000 cases we need data of the order of 10,000 cases with about ten* deaths before we can make any statements as to the death rate of that agent.

If the death rate of anesthetic agent B is 1:10,000 cases we need the order of 100,000 cases with, again, about ten instances of death attributable to the agent, in order to make any statement as to the death rate of that agent.

It is sometimes said that the death rate directly attributable to ether anesthesia is 1:10,000. In order to prove that another agent is better than ether in this respect, we must have, then, not less than about 100,000 cases of the other agent, under comparable conditions, if we are to *prove* that the other agent excells or even equals ether as far as death rate is concerned.

Stating the foregoing in general terms, we must deal with so many cases that the square root of the number of deaths is not greater than about one-third of the number of deaths.†

More attention to these points would cut down on the frequency with which institutions advocate a given anesthetic agent or a given procedure only to have abandoned that procedure or that agent by the time the report concerning it gets into print.

CONCLUSIONS

New drugs for general anesthesia must be tested by constant criteria if they are to be compared with established agents. The irreducible minimum of simple, arbitrary requirements of the ideal general anesthetic agent is described. Important from the point of view of physical and chemical qualities are: Potency or narcotic strength; solubility in air and blood; and explosibility. From the more strictly biologic aspect of the question, the elements of importance are: Controllability of the route of administration; side-effects and toxicity of action; adequacy of physiologic effects for the

* It might be argued that six deaths are adequate; however, for a conservative estimate ten are safer.

† I am indebted to Professor E. B. Wilson for advice here.

task at hand; specificity of action; elimination. Statistical requirements are considered in relation to the mass of data necessary to permit dogmatic statements to be made as to death rate and general safety. The use of these criteria is illustrated by testing the common anesthetic agents.

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TRENDS IN INHALATION ANESTHESIA*

WESLEY BOURNE, M.D.
MONTREAL, CANADA

THE TRANSCENDENT PRINCIPLE of reversibility in anesthetic action, wherein perception by the senses may be suspended and restored, constitutes a boon to man, and since the universal adoption of inhalation anesthesia nearly 100 years ago, the scope of laboratory investigation has increased and the arm of surgery in humane rescue extended.

It was not long, however, before the ill effects which anesthetics are capable of producing became apparent; indeed, as early as January, 1849, in Magdeburg, Dolhoff[1] observed delayed chloroform poisoning. The ravages of this drug are so well known that it might be numbered among Erasmus' *inverse Sileni of Alcibiades.* Any time these hundred years, an important trend has been to disclose completely the influences of anesthetics on vital processes, and numerous data exist concerning the effect of anesthetics upon metabolism, as represented by blood findings, liver changes and the composition of the urine. The facts have been recounted elsewhere[2, 3] and it is not practical, at this time, to do more than generalize discursively.

With regard to the effects of inhalation anesthesia on the blood, two of them have clinical significance, namely, concentration and acidosis. Chloroform and ether cause marked blood concentration, which is due chiefly to the migration of water from the blood to the tissues. This blood concentration is adequately lessened by the administration of water or dilute solutions, and everybody knows how readily these are absorbed in proportion to the depth and duration of the narcosis. By analogy, it would seem that the degree of concentration is not nearly so great with the gases, nitrous oxide, ethylene and cyclopropane; at least there is nothing like the same avidity for fluids. The tendency of late, therefore, is to employ the gases more and more and especially in the case of the dehydrated patient. It may be mentioned, that from the falling-drop fundamental of Barbour and Hamilton,[4, 5] "the advent of a method by which blood and plasma specific gravity changes can be followed from minute to minute, with single drops, opens a field of application to very acute shifts in the water balance, such as occur, for instance, in anesthetic and operative shock. One can also evaluate procedures designed to combat these conditions, such as the administration of morphine or alkalis. The method further permits following the administration of fluids in various acute toxemias. While fluids are actually being given, the blood condition can serve as a guide to the therapeutic procedure. Anesthetic shock, as the trend of recent investigation shows, is closely bound up with acidosis and anhydremia. It is possible that in this instance the water content of the blood is

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

of equal if not greater importance than blood pressure." Determinations along these lines are now being made at the Presbyterian Hospital, New York City,[6] and in Montreal, by O'Shaughnessy and myself at St. Mary's Hospital. It is hoped soon to obtain some valuable information.

It has been shown that the acidosis of anesthesia is a true acidosis, that is, the alkali reserve is lowered and the hydrogen ion concentration is increased; that phosphoric and lactic acids are discharged from the muscles, in part held in the liver until the resumption of kidney function after recovery, and then in some measure redistributed as well as excreted. It has been shown, too, that this acidosis may be lessened by building up the glycogen reserves of the body before a surgical operation, and that the acidosis of anesthesia may be reduced considerably by the rectal administration of copious quantities of a specially balanced hypotonic alkaline sodium and potassium phosphate solution immediately after operation. This bulky, watery, and alkaline solution not only obviates the acidosis, but decreases the blood concentration; and also ameliorates the patient's condition during recovery by virtue of its potassium ions, said to be the most stimulating of all to any depressed living thing, especially when the phosphate anion is present and when the medium is alkaline. Although I disapprove the use of glucose solutions during operation for the simple reason that at this time hyperglycemia is apt to be present, I commend their employment before operation and after complete recovery from anesthesia. A trend in inhalation anesthesia is to allow fluids to be diffused more freely. Let us liken them to the healing waters of the Onchestus described by Aristotle.

In olden times the liver was thought to be the seat of love or lust and in this manner the father of Euphuism, the Oxonian, John Lyly, of Elizabethan days, made mention of it in his Endymion as: "It tickleth not my liver." Whether or no it be true that such passion saps vitality, we must now behold the liver with other than amatory eye. The liver is a prodigious organ, possessed of multiform activities, assimilatory and secretory, diurnal and rhythmical.[7] However, despite its magnitude and physiologic importance, its cells are exceedingly susceptible to injury, so that in the very performance of their duties they are apt easily to succumb. But their regenerative powers are remarkable. As long ago as when the Pasteur Institute was founded (1886), Bizzozero[8] and von Podwyssozki,[9] separately, showed that loss of liver substance is replaced by proliferation of the liver cells and the cells of the small bile ducts. Confirmation and amplification have been given to this by several other observers, and Mann and Magath[10] demonstrated that about 70 per cent of the dog's liver may be removed without serious damage to the portal and vena cava circulation. In a few months the remainder will be enlarged and the amount of tissue practically the same as before operation. What a prolific regeneration! The Ancients must have had some conception of this when they told of Prometheus chained on Mount Caucasus and subjected to the daily attack of an eagle (probably a vulture) which, for ages, preyed upon his liver, yet succeeded not in consuming it. Let us say with

Carlyle, that the minds that made such stories are here yet. How strangely things grow, and die, and do not die! It is well that there is such an excess of liver tissue and that its cells are so readily capable of karyokinetic multiplication; but in the instance of poisoning, as from chloroform or phosphorus, notwithstanding liver regeneration and the normal appearance of the tissue under the microscope, it has been proved, since the introduction of the dye tests, that complete functional recovery is not fully established for some considerable time later. A trend has been, therefore, to compare the effects of anesthetics on the liver by employing the bromsulfalein detoxification test. Suffice it to say that chloroform is maximally damaging to the liver, ethyl ether and vinyl ether slightly so, and the gases, nitrous oxide, ethylene and cyclopropane, in themselves, not in the least harmful. But when there is not an adequate supply of oxygen during the anesthesias of chloroform and the ethers, the liver function impairment is markedly enhanced, and in the instances of the gases, nitrous oxide and ethylene, there will be considerable injury. Such does not prevail in cyclopropane anesthesia as a superabundance of oxygen is always given. From a consideration of the effects of anesthetics on the liver, we learn to eschew chloroform and to avoid anoxia. At this conjuncture, it is apposite to draw attention to the destructive change in the brain when asphyxia accompanies nitrous oxide anesthesia, so explicitly described by Courville.[11, 12]

The changes which anesthetics may produce in the kidney seem to be analogous to, and concurrent with, those in the liver. It has been known for a long time that anesthesia, generally, diminishes the volume of the urine secreted. From various observations, it may be said that all inhalation anesthetics cause some depression of kidney activity, whereby the rate of secretion and composition of the urine is lowered; that the degree of depression varies directly with the depth of narcosis; and that the effects are influenced by the condition of the kidneys, by the water content of the blood, and by the duration of the anesthesia. Even during cyclopropane anesthesia, Waters and Schmidt[13] have shown that the urinary output is usually suppressed and a compensatory increase occurs several hours following.

From these desultory remarks concerning the interferences with metabolism which anesthetics may bring about, it can be seen that the trend has been to employ less toxic drugs, to use combinations of them, to improve the methods of their administration, and to offset and alleviate their deleterious actions, for by how much the more these *principia* are observed, by so much the more will surgery be endured. Thus it was that ethylene and cyclopropane, in their times, were brought forward; thus it is that Lundy[14] has stressed the principle of combining regional and general anesthesias, and quite recently[15] recommends pentothal sodium intravenously for inducing anesthesia, especially in hypersensitive individuals, to decrease the stages of excitement and avoid cyanosis, particularly in cases of high blood pressure—this is an excellent procedure, and I am pleased to have followed it; thus it is that intratracheal methods were developed to prevent obstructions to breathing

and to produce quiet respiration; thus, too, it is that the use of fluids has increased and oxygen is given so freely.

While we must be very careful continually to remember the beneficial actions of inhalation anesthetics, we cannot but admit their limitations, and comprehensively the trend is to select those anesthetic agents and methods of administration that are least harmful. In the light of our present knowledge, it would seem rational to choose one of three procedures: namely, regional anesthesia, that is, "local," on one of the various forms of "block" anesthesia, or "spinal"; or general anesthesia with nitrous oxide or cyclopropane; or a combination of the two. All other forms of anesthesia seem doomed soon to desuetude, at least in major surgery. I admit at once that the advantages of spinal anesthesia are very great, particularly on account of the muscular relaxation and the excellent recovery; particularly, too, for surgery of the upper abdomen and in thoracic surgery. Perhaps the devotees of inhalation anesthesia are inclined to regard this as an adverse trend.

The all-pervading desire for improvement and the increasing demands of surgery continually give tendency to change in anesthesia, and cynosures in this regard, of late, are the employment of cyclopropane, the absorption of carbon dioxide, and the administration of anesthetics by the closed intratracheal technic. The advantages of cyclopropane are already too well known for me to be prolix in the matter, but it may be said that a splendid combination is avertin per rectum, to the patient in bed, half an hour before operation, followed in the operating room by a mixture of cyclopropane, nitrogen and oxygen. The removal of carbon dioxide from the expired air permits the continued and repeated use of anesthetic materials. The closed intratracheal method precludes respiratory obstruction; obviates interference with some surgical procedures; gives absolute assurance of a plentiful supply of oxygen directly to the lungs; affords quieter breathing and a softer abdomen, although narcosis is not profound; and supplies the ready application of Guedel's method of artificial control of respiration. Observing all due precaution against making arbitrary arguments, one might go on to relate other examples. Even a casual review of recent literature suggests, here and there, the influence of these centers of attraction, direct or indirect, upon the practice of inhalation anesthesia.

In the general course which inhalation anesthesia is taking, one notices the increasing attention paid to the preparation of the patient for operation. We cannot be too careful in this direction; indeed, we are still too much inclined to neglect some of the important considerations and to hasten the matter. One thing that I do feel we should be more particular about is the problem of fear, so shamefully disregarded, especially in larger institutions. Fear may lead to phantasmagoria of excruciating incident to the patient going under an anesthetic, something like the wild ideas in the land of dreams depicted by Edgar Allan Poe in some of his weird but beautifully written tales of mystery and imagination. This source of terror may lead to severe shock, or at least to a tremendous dissipation of nervous energy. Remember the

almost prophetic words of Oliver Wendell Holmes, that "it is better to lose a pint of blood from your veins than to have a nerve tapped. Nobody measures your nervous force as it runs away, nor bandages your brain and marrow after the operation." How aptly this thought implies that we ought to do all in our power to assuage fear in one to whom an operation is proposed, by the cultivation of a psychologic approach intended to inspire confidence, gain reliance, and induce harmonious contentment. In fine, the anesthetist does well to take upon himself the rôle of μουσικὸς, that is, as Plato meant it in the broader sense.

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ANOXIA*

A SOURCE OF POSSIBLE COMPLICATIONS IN SURGICAL ANESTHESIA

ROY D. MCCLURE, M.D., F. W. HARTMAN, M.D.,
J. G. SCHNEDORF, M.D., AND VICTOR SCHELLING, PH.D.
DETROIT, MICH.

FROM THE DEPARTMENT OF SURGERY AND THE DEPARTMENT OF LABORATORIES, HENRY FORD HOSPITAL, DETROIT, MICH.

THE RECENT WORK of Courville[1] on "Asphyxia as a Consequence of Nitrous Oxide Anesthesia," and the pathogenesis of the cerebral narcosis resulting from the same, have served to concentrate interest and increase knowledge of the whole field of asphyxia or anoxia in which the physiologists, led by Yandell Henderson,[2] Barcroft,[3] and others, have been pioneering for years. The anesthesiologists Schmidt,[4] Shaw, Steele and Lamb,[5] Seevers and Waters,[6] Raginsky and Bourne[7] and others have probably followed the physiologists most closely as evidenced by their more recent contributions. On the other hand, the pathologists have been slow to interest themselves and correspondingly less helpful in the recognition of the gross and microscopic lesions despite the admonition of Henderson that "asphyxia is the most frequent and most important of all pathologic processes. A large part of all the structural abnormalities that the pathologist studies involve perversions of tissue respiration."

Courville[8] sums up his observations as follows: "As a rule these patients developed respiratory or cardiorespiratory failure while under nitrous oxide-oxygen anesthesia and failed to regain consciousness when the anesthetic was withdrawn. During the survival period the patients remained in coma, frequently had convulsions and most of them died in a state of hyperthermia after an interval of 1½ to 26 days. A few individuals recovered, some with a residual lenticular syndrome, others with a permanent psychosis, while some fortunately recovered completely. In the fatal cases the cerebral cortex and the lenticular nuclei presented areas of necrosis which at times became confluent and if a survival period was sufficiently long, resulted in astrovascular scars." Thus a classical picture of anoxia is drawn which may apply equally well to the condition produced by the various narcotics and anesthetics, or their combinations.

Oxygen want occurring with nitrous oxide anesthesia (Brown, Easson, Lucas and Henderson[9]) is readily appreciated because it is necessary to administer 80 per cent to 95 per cent concentration of this gas to get good anesthesia, thus reducing the arterial oxygen tension directly at first and later by depression of the respiratory center, producing anoxic anoxia. The other types of anoxia—anemic, due to lack of, or inactivation of, hemoglobin, decreasing its capacity to take up oxygen; stagnant, due to retardation of the

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circulation and transportation of oxygen; and histotoxic, due to drugging of the tissue cells so that they cannot utilize the available oxygen—are to be kept clearly in mind. As this study will demonstrate, it is usually a combination of all or several of the types which results in serious complications.

The following case illustrates all types of anoxia with fatality.

Case 1.—A white, unmarried female, with bilateral pulmonary tuberculosis and secondary anemia, was treated by pneumothorax. The last pneumothorax was performed July 14, 1938, when 375 cc. of air was introduced into the left pleural spaces. Adenoidectomy was performed July 15, 1938, with nembutal 1½ gr. morphine sulphate 1/6 gr., and atropine 1/200 gr. as preoperative medication and nitrous oxide-oxygen anesthesia. The anesthesia lasted only 20 minutes but obvious cyanosis persisted throughout. The patient's condition was satisfactory when she was returned to her room an hour later but she was still unconscious and cyanotic. One hour later respirations became labored and soon stopped. *Anatomic Diagnosis:* Asphyxia—blood uncoagulable; fibrocaseose tuberculosis, bilateral; chronic salpingitis. In this case the pneumothorax 24 hours previously and the nitrous oxide would account for anoxic anoxia; the secondary anemia for anemic anoxia; the surgical procedure for the low blood pressure and stagnant anoxia; and the preoperative medication nembutal and morphine for histotoxic anoxia.

The stagnant type of anoxia is well illustrated by two cases of splanchnic resection for hypertension. The procedure resulted in immediate reduction of systolic blood pressure, in the first case of 158 points and in the second of 116 points.

Case 2.—White, female, age 45, married, no children. Complaint: Dizziness. Present illness: Approximately one year ago began having intermittent attacks of dizziness and vomiting. Last attack three weeks ago. Past history: Pelvic operation in 1926. *Physical Examination:* Heart enlarged, heart sounds roughened. Vessel walls moderately thickened. Blood pressure 214/142, pulse 104. Red blood count 4,340,000, hemoglobin 11.1 Gm. Urine: Specific gravity 1.018, trace of albumin. Wassermann negative. Phthalein test 52 per cent in two hours. *Impression:* Essential hypertension, cardiac hypertrophy, retinal hemorrhages, generalized arteriosclerosis. Transferred to Neurosurgery for splanchnic resection, bilateral.

Preoperative preparation: Morphine sulphate ¼ gr., scopolamine 1/100 gr. Operation, July 15, 1937. Duration of operation three and one-half hours. Blood pressure at beginning of operation 225/110, at end of operation 100/90. Returned from operation in fairly good condition. Pulse regular,. rate 82; respirations 24; blood pressure 67/53. Twenty-four hours after operation, pulse 92, respirations 24, blood pressure 128/72. Drowsy, had difficulty in swallowing and speaking. Left facial paralysis. Impression at this time: Cerebral anemia as the result of marked and sudden reduction of blood pressure. July 20: Facial paralysis persists and weakness is present in left lower extremity. Also blurring of vision. July 22: Patient still mentally confused. July 25: Blood pressure 165/105. Paralysis somewhat improved. Discharged the fourteenth day.

Case 3.—White, female, age 51. Complaint: Headaches, dizziness and nausea. Present illness: Has been told frequently that she has high blood pressure. Past history: Frontal and temporal headaches; has had "nervous breakdown." *Physical Examination:* Undernourished and pale. Heart moderately enlarged. Blood pressure 256/150. Arterial walls thickened. Red blood count 3,850,000, hemoglobin 12.2 Gm. Phthalein 28 per cent in two hours. *Impression:* Hypertension, generalized arteriosclerosis, mitral heart disease, spastic colon. Transferred to Neurosurgery for operation.

Preoperative preparation: 4.7 mg. avertin. Operation, January 9, 1937, under nitrous oxide: Bilateral splanchnic resection. Blood pressure at beginning of operation 236/130,

at end of operation 150/100. Returned from the operation in fair condition. Pulse 76, respirations 22, blood pressure 120/90. January 10 and 11: Condition fairly good. Blood pressure 140/86. January 12: Râles at both lower lobes. *Impression:* Pulmonary edema. January 14: Patient unconscious. January 24: Chest condition improved, no cyanosis. Muttering delirium. February 23: Discharged from hospital. July 24: Patient in wheel chair. Definite mental confusion. Talked very little, did not recognize doctors, did not know where she was and did not answer questions satisfactorily. Agitated and restless. Blood pressure 150/110.

Several types of anoxia are possible in the last case, but in view of observations to be presented later it is felt that the histotoxic type produced with the preoperative sedation of 12 gr. of sodium amytal was the predominant factor.

Case 4.—Colored, female, age 32. Complaints: Pelvic pain. Physical examination reveals salpingo-oophoritis, bilateral; cystic right ovary; multiple fibroids of uterus. Admitted to Gynecologic Service for operation, August 31, 1932.

Preoperative orders include sodium amytal 3 gr., 10 P.M.; sodium amytal 6 gr., 6:30 A.M.; sodium amytal 3 gr., 8:15 A.M., when called to operating room. Operation performed under ether, oxygen and ethylene. Operation: Appendicectomy, hysterectomy, and bilateral salpingo-oophorectomy, lasting one hour and 25 minutes. Following the operation the patient received pantopon 1/3 gr. q 3 h; glucose 10 per cent and normal saline intravenously. Consciousness was not regained following the operation, and a neurologic consultation resulted in a diagnosis of protracted ether narcosis. September 10: Threshold of consciousness seemed to be slightly raised but motor coordination in the right lower extremity was disturbed. September 14: Right-sided hemiparesis was evident. September 15: Transferred to Neurologic Service for treatment. By October 1, there was some improvement; patient was conscious but answers to questions were unintelligible. Discharged from hospital, January 13, 1933, four and one-half months after operation, with some improvement in speech but with residual paralysis on right side. *Final Diagnosis:* Hemiplegia right (residual from prolonged narcosis).

These cases not only illustrate the various types of anoxia resulting in serious complications but they demonstrate that such complications may readily occur without either cardiovascular or respiratory failure during the anesthetic. It is fully recognized that cessation of respiration or circulation for five or ten minutes may produce extensive degenerative changes in the central nervous system and perhaps other organs. However, the data presented here emphasize that similar changes may result from reduction of oxygen tension, transportation or utilization, without interruption of respiration or circulation.

For convenience in considering the anesthetics most commonly used in our institution they may be divided into seven groups: Ether, ethylene and oxygen, cyclopropane and oxygen, nitrous oxide and oxygen, avertin, procaine (spinal), evipal and other barbiturates. Much of the current work, including our own, on anesthesia is pure animal experimentation, but the observations on patients to be reported were made during the routine operative procedure; hence it is impossible to give results on the anesthetic agents alone, uninfluenced by the factor of preoperative medication. In view of this, the barbiturates which are now frequently used preoperatively as sedatives and narcotics will be discussed first.

The pharmacologic action of the barbituric acid compounds is described by Edmonds and Gunn[10] as being essentially sedative and hypnotic, and Keeser and Keeser[11] found that they tend to localize in the diencephalon rather than the cerebral hemispheres. In addition to the cerebral action, a fall in body temperature, respiratory depression and an initial circulatory depression are usually noted. As intravenous anesthetics they are considered dangerous because the necessary dosage approaches the lethal one. For preoperative medication, only the short acting preparations are to be employed if pulmonary complications resulting from prolonged respiratory depression and postoperative manias are to be avoided.

TABLE I

EFFECT OF PREOPERATIVE MEDICATION ON RESPIRATION OF CEREBRAL CORTEX

No.	Amount of Drug	Q O_2 in Cm. Per Mg. Dry Weight Per Hour		Percentage Decrease
		During	After	
	Seconal 5%			
1	2.1 cc.	1.6224	2.2702	28
2	2.1 cc.	1.4624	2.0455	28
	Nembutal 3.33%			
3	1.2 cc.	2.8607	3.7616	23
4	1.6 cc.	3.2421	3.8735	16
	Morphine			
5	½ Gr.	2.6474	3.4721	23
6	½ Gr.	2.330	3.0452	23
	Sod. Amytal 10%			
7	0.8 cc.	2.6471	3.3658	21
8	1.0 cc.	2.398	3.3416	28

TABLE II

EFFECT OF PENTOBARBITAL NARCOSIS UPON BRAIN METABOLISM

(*Av. Three Dogs*)

Blood Gas Analysis	Normal Unanesthetized	Pentobarbital* Narcosis	
		0.5 Hr.	4 Hrs.
Carotid Artery			
O_2 content	16.9	12.4	15.5
O_2 capacity	18.2	18.4	18.4
O_2 saturation	93.3	68.8	84.6
CO_2 content	40.6	49.0	42.5
Jugular Vein			
O_2 content	14.0	10.3	12.9
CO_2 content	45.4	51.4	45.0
O_2 utilized (AO_2–VO_2)	2.9	2.1	2.6
CO_2 produced (VCO_2–ACO_2)	5.4	1.1	2.5

* 30 to 35 mg. per Kg. body weight, intravenous.

It is interesting to hear the pharmacologists warn against pulmonary and cerebral complications, since cerebral necrosis and hemorrhagic pneumonia have been described in our earlier communications[12,13] in both the experimental animal and patients when given fever therapy under heavy barbiturate sedation. Similar lesions have been produced in animals with these preparations alone. Jowett and Quastel[14] have shown that luminal and evipal decrease or abolish the utilization of oxygen by brain slices. This work has been recently confirmed and extended in our laboratories working with sublethal doses of popular barbituric acid derivatives (Table I). Comparable inhibition of oxidation in liver, kidney and muscle by narcotics has been demonstrated also by Jowett and Quastel.[14]

TABLE III

Evipal Narcosis
Dosage 60 to 70 Mg. Per Kg.

	Arterial Blood Oxygen 0.5 Hr.		
Dog	Cont.	Cap.	Sat.
1	12.8	20.1	63.8%
2	16.5	19.6	84.0
3	11.5	15.1	76.6
4	13.2	15.9	83.4
5	14.3	17.5	81.5
6	11.8	15.5	76.0
Average	13.3	17.2	79.2

TABLE IV

Seconal Narcosis
Dosage 10 to 15 Mg. Per Kg.

	Arterial Blood Oxygen 0.5 Hr.		
Dog	Cont.	Cap.	Sat.
1	15.4	18.3	82.0%
2	14.5	16.9	86.3
3	11.3	15.3	74.0
4	12.8	18.1	70.8
5	12.9	15.7	82.2
6	13.5	16.2	83.0
Average	13.4	16.7	79.7

Brain metabolism *in vivo* under pentobarbital narcosis is shown in Table II. The oxygen content at the end of 30 minutes in the carotid artery is decreased 25 per cent, the oxygen capacity remains the same, the oxygen saturation is reduced 24 per cent, and the CO_2 content is increased 20 per

cent. In the jugular vein, 30 minutes after administration, the oxygen content is reduced nearly 33 per cent and the CO_2 content has increased 10 per cent. The oxygen utilized fell 28 per cent and the CO_2 produced fell 80 per cent.

TABLE V
Sodium Pentobarbital Narcosis
Dosage 30 to 35 Mg. Per Kg. I. V.

	Arterial Blood Oxygen					
	0.5 Hr.			4 Hrs.		
Dog	Cont.	Cap.	Sat.	Cont.	Cap.	Sat.
1	13.1	20.2	65.2%	16.1	20.2	79.9%
2	13.1	17.3	78.3	14.9	17.3	86.3
3	11.1	17.6	63.0	15.4	17.6	87.7
4	14.6	18.3	79.8	16.4	18.3	89.9
5	14.7	19.0	77.5	16.3	19.0	86.2
6	11.2	16.8	66.0	14.8	16.8	88.2
Average	12.9	18.2	71.6	15.6	18.2	86.3

TABLE VI
Sodium Amytal Narcosis
Dosage 30 to 35 Mg. Per Kg. I. V.

	Arterial Blood Oxygen								
	0.5 Hr.			4 Hrs.			7 Hrs.		
Dog	Cont.	Cap.	Sat.	Cont.	Cap.	Sat.	Cont.	Cap.	Sat.
1	18.9	20.8	91.0%	18.9	20.8	91.0%	—	—	—
2	15.5	18.9	82.3	14.6	18.9	77.2	17.8	18.9	94.6%
3	16.0	18.9	84.8	13.1	18.9	69.6	17.4	18.9	92.4
4	14.5	17.4	83.7	15.7	17.4	90.6	—	—	—
5	22.1	24.7	89.5	—	—	—	—	—	—
6	21.3	24.5	87.1	—	—	—	—	—	—
Average	18.0	20.8	86.4	15.5	19.0	82.1	17.6	18.9	93.5

TABLE VII
Dial Narcosis
Dosage ½ Cc. Per Kg. I. P.

	Arterial Blood Oxygen								
	1 Hr.			2.5 Hrs.			7 Hrs.		
Dog	Cont.	Cap.	Sat.	Cont.	Cap.	Sat.	Cont.	Cap.	Sat.
1	13.9	16.5	84.6%	16.0	18.2	88.0%	18.7	20.0	93.5%
2	15.3	17.2	89.5	15.0	17.2	87.4	19.2	21.1	91.4
3	14.4	16.7	86.0	15.8	17.2	92.0	17.2	19.6	88.7
4	16.3	17.6	92.5	15.8	17.7	89.2	17.2	18.6	92.0
5	15.8	18.1	87.5	—	—	—	—	—	—
6	13.0	15.0	86.6	—	—	—	—	—	—
Average	14.7	16.8	87.7	15.6	17.5	89.1	18.0	19.8	91.4

Tables III, IV, V, VI and VII, showing arterial blood values in the dog under therapeutic doses of evipal, seconal, sodium pentobarbital, sodium amytal and dial, demonstrate that there is a consistent depression of the oxygen saturation ranging from 10 to 30 per cent with the lowest values produced by the shorter acting evipal, seconal and sodium pentobarbital.

TABLE VIII

SECONAL GR. 6

Patient	Age	Duration Min.	Arterial Blood Oxygen			Blood Pressure	
			Cont.	Cap.	Sat.	Normal	Sedat.
N. F.	55	75	17.8	22.3	79.7%	158/70	150/60
V. B.	16	30	16.6	17.7	93.5	120/80	116/80
L. K.	60	30	18.2	19.9	91.5	212/110	185/106
B. W.	32	30	14.0	16.0	87.8	120/70	110/80
I. R.	31	90	18.1	21.7	83.5	116/70	115/85
M. W.	51	90	15.4	17.8	86.5	140/90	112/80
M. R.	41	30	18.2	21.0	86.7	150/82	128/100
M. B.	19	30	16.7	19.3	86.5	124/82	120/80
B. C.	60	45	12.4	14.5	85.8	158/80	144/88
S. K.	64	60	17.5	20.0	87.9	140/80	114/70
M. B.	20	60	16.0	18.1	88.6	120/70	

TABLE IX

CYCLOPAL GR. 10

Patient	Age	Duration Min.	Arterial Blood Oxygen			Blood Pressure	
			Cont.	Cap.	Sat.	Normal	Sedat.
M. H.	54	60	17.1	19.7	86.5%	142/75	102/70
M. B.	54	90	16.4	18.3	89.5	175/90	120/70
J. H.	29	60	15.9	19.0	83.7	135/80	115/75
E. B.	47	120	7.8	10.5	74.7	136/76	130/78
C. R.	51	45	16.2	20.3	79.8	140/96	140/96
E. H.	32	30	12.9	15.9	81.2	—	—
A. B.	28	30	18.6	21.0	88.5	—	—

Tables VIII and IX illustrate the effect of seconal and cyclopal respectively, given as preoperative medication on the oxygen saturation of the arterial blood and blood pressure. There is a uniform reduction in the oxygen saturation of from 5 to 20 per cent and usually a reduction in blood pressure ranging from 0 to 40 points systolic and 0 to 20 points diastolic.

From these data it seems clear that the barbiturate derivatives in moderate dosage produce slight to severe anoxia. This anoxia is due to respiratory depression (anoxic anoxia), circulatory depression (stagnant anoxia) and reduction of cellular respiration (histotoxic anoxia). Within the therapeutic range, histotoxic anoxia is most important in barbiturate sedation or narcosis, since brain slices have the utilization of oxygen reduced 16 to 28 per cent and the brain *in vivo* has its oxygen utilization reduced 28 per cent and its CO_2 produced reduced 80 per cent.

Avertin or tribromethanol has the chemical structure of ethyl alcohol with the substitution of three bromine atoms, and its narcotic effect is comparable to that of chloroform, according to Sollmann.[15] The preparation usually employed is avertin solution, that is one Gm. of avertin dissolved in one cc. of amylene hydrate, which is also an active narcotic. The pharmacologic action from clinical dosage includes marked depression of the respiratory center with decrease in rate and diminished response to CO_2. Parsons,[16] Greer,[17] and Kennedy[18] show that the blood pressure may be sharply depressed about eight minutes after administration due to vasodilatation, decrease in blood volume and depression of the heart. Table X shows the reducing effect of avertin solution on the oxygen utilization of brain slices ranging from 10 to 14 per cent.

TABLE X

EFFECT OF PREOPERATIVE MEDICATION ON RESPIRATION OF CEREBRAL CORTEX

No.	Amount of Drug	Q O_2 in Cm. Per Mg. Dry Weight Per Hour		Percentage Decrease
		During	After	
	Evipal 10%			
1.....	2.0 cc.	1.9268	2.4151	22
2.....	1.5 cc.	1.9288	2.3822	19
3.....	1.0 cc.	2.4872	3.0971	19
4.....	1.2 cc.	2.8081	3.5693	21
5.....	2.0 cc.	2.0549	2.545	19
	Avertin 1.5%			
6.....	35 cc.	3.1294	3.4673	9.7
7.....	40 cc.	2.819	3.2924	14
8.....	42 cc.	2.9745	3.3807	12

TABLE XI

Avertin Narcosis
Dosage 180 Mg. Per Kg.

Dog	Arterial Blood Oxygen		
	Cont.	0.5 Hr. Cap.	Sat.
1.....	13.7	17.1	80.2%*
2.....	19.0	21.4	88.6
3.....	17.9	20.1	89.4
4.....	19.5	21.5	91.2
5.....	15.3	22.3	68.5†
6.....	17.1	20.4	84.1
Average.....	17.0	20.4	83.6

* N.B.P. 170/90; narcosis 100/55.
† R = 4 min.; deep narcosis.

Table XI shows the reduction in the oxygen saturation of the arterial blood in avertin narcosis in the dog resulting from 180 mg. per Kg. The percentage of reduction varies from 3 to 25 per cent, the average being 10 per cent. The first animal exhibited a fall of 70 points in systolic blood pressure and 35 points in diastolic blood pressure. In the fifth animal, the respiratory rate fell to four per minute and was accompanied by deep narcosis and the sharpest reduction in the oxygen saturation of the arterial blood.

TABLE XII

AVERTIN NARCOSIS

Patient	Age	Sedation Avertin	Duration Min.	Arterial Blood Oxygen			Blood Pressure	
				Cont.	Cap.	Sat.	Normal	Anesth.
J. B.....	32	90 mg./Kg.	30	17.0	19.2	88.7%		
M. L.....	35	80 mg./Kg.	45	18.0	20.4	88.0	202/134	140/90
M. C.....	45	70 mg./Kg.	60	18.9	20.7	91.2	160/60	180/100
T. H.....	61	70 mg./Kg.	30	16.9	18.9	89.2	150/85	100/60
B. H.....	54	80 mg./Kg.	30	15.4	17.6	87.7	126/70	90/60
H. P.....	30	80 mg./Kg.	45	16.6	19.5	85.2	124/70	120/50
L. Mc....	42	70 mg./Kg.	45	13.3	17.6	75.5	110/60	100/60
L. B.....	66	70 mg./Kg.	30	13.5	14.8	91.6	140/60	100/60
T. de P...	28	80 mg./Kg.	30	15.0	16.7	89.6	130/82	100/80
A. C.....	32	85 mg./Kg.	20	17.5	19.8	88.4	156/86	150/80

Table XII shows the oxygen saturation of ten patients under avertin anesthesia, ranging from 3 to 20 per cent below normal. The blood pressures were taken after the critical period, eight minutes following administration, but show consistent reduction in systolic pressures ranging from 4 to 62 points, and in diastolic pressures ranging from 0 to 44 points. It is to be noted that none of these patients received other preoperative medication which might account for the relatively good record shown. The anoxia in this instance is charged to depression of the respiratory center with slowing of the rate (anoxic anoxia), to the reduction in blood pressure and vasodilatation (stagnant anoxia) and, to a small degree, to histotoxic anoxia, as the utilization of oxygen by brain slices is depressed from 10 per cent to 14 per cent, or less than half seen with the barbiturates.

The recent contributions on spinal anesthesia by Seevers and Waters,[6] Schubert,[19] Shaw, Steele and Lamb,[20] and Nowak and Downing[21] make it impossible to add anything except observations upon patients under actual operative conditions.

All of our patients (Table XIII) had preliminary sedation with morphine sulphate or barbiturates. Some of the oxygen saturation values are within the normal range and the greatest reduction was 10 per cent. In view of the data presented above, the slight changes are attributed to the effect of preoperative medication alone. There is a fall in blood pressure in each case which is routinely combated by ephedrine and oxygen inhalations. Seevers

and Waters[6] observed that "a considerable decrease in alveolar, as well as in arterial and venous blood oxygen occurs, with a corresponding increase in CO_2." This result they attribute to "initial decrease in peripheral resistance to blood flow; vasomotor nerve and skeletal muscle paralysis; decrease in minute volume respiration accompanying intercostal nerve paralysis; inadequate oxygenation of blood; diminished minute volume blood flow; progressive loss of vascular tone over the whole body and acute cardiac incompetence; and failure of the medullary respiratory mechanism." Schubert[19] found no definite changes in oxygen consumption in man; the arteriovenous difference was increased; and the cardiac output and blood pressure fell. Shaw, Steele and Lamb,[20] in dogs, found a perfectly saturated arterial blood and a lowered oxygen content of the venous blood or an increased arteriovenous difference indicating stagnant anoxia. They believe that this anoxia will vary with the extent of the area anesthetized or the magnitude of the vasoconstrictor paralysis and vasomotor compensation. Nowak and Downing,[21] working with cats under light ether anesthesia, found spinal anesthesia did not depress the arterial oxygen; however, the venous oxygen content was reduced, resulting in an increased arteriovenous oxygen difference. They suggest that fatal accidents are due to paralysis of the phrenic mechanism or respiratory center, or both. There is substantial agreement between three of the four workers quoted, and their conclusion that there is no substantial reduction in arterial blood oxygen when the cardiovascular depression is combated, corresponds with our observations in anesthetized patients.

TABLE XIII

SPINOCAINE (SPINAL)

2.5 TO 3 CC.

Patient	Age	Sedation	Duration Min.	Arterial Blood Oxygen			Blood Pressure		
				Cont.	Cap.	Sat.	Normal	Anesth.	
L. K.	31	Nembutal Gr. 1½ M.S. Gr. ¼	60	21.2	22.4	94.5%	134/78	120/80	
S. S.	56	M.S. Gr. ¼	90	16.4	19.3	83.2	130/80	88/50	
F. T.	53	Seconal Gr. 3	60	18.9	20.4	92.7	126/82	100/70	
H. L.	22	M.S. Gr. ¼	60	21.3	23.7	89.9	140/86	130/90	
G. P.	34	M.S. Gr. 1/6	90	20.6	22.6	91.5	125/75	90/70	
S. M.	32	Seconal Gr. 3	120	18.4	21.1	87.5	120/90	86/60	
G. S.	39	Seconal Gr. 3	90	20.3	22.7	89.4	106/70	100/70	
J. B.	41	Seconal Gr. 3	120	19.0	21.8	86.7	140/92	100/70	Eph. 150/90
A. S.	43	Seconal Gr. 3	15	16.1	19.0	84.9	140/76	80/50	Eph. 110/80
O'C.	32	Seconal Gr. 3	60	19.6	21.2	88.0	118/20	100/66	

Nitrous oxide was the first inhalation anesthetic and it acts partly by direct narcotic effect upon the central nervous system, but to a greater extent through the exclusion of oxygen. The action is perhaps best illustrated by Clark (from Sollmann[15]) in Table XIV.

When nitrous oxide is combined with air or oxygen it produces almost a pure anoxic anoxia by the exclusion of oxygen from the inspired mixture. When combined with preoperative medication the latter brings in both the

TABLE XIV

Vol. %			Degree of	
N_2O	O_2	Depth of Anesthesia	Asphyxia	Relaxation
80	20	Subconscious analgesia	None	None
86	14	Complete analgesia	None	None
89	11	Partial anesthesia	Slight	Slight
94	6	Complete anesthesia	Dangerous	Partial

TABLE XV

NITROUS OXIDE AND OXYGEN

Patient	Age	Sedation	Duration Min.	Arterial Blood Oxygen Mother Cont.	Mother Cap.	Mother Sat.	Baby Sat.
K. T.	22	None	140	12.1	19.4	62.4%	49.9%
B. A.	40	Seconal Gr. 6	15	16.2	19.4	83.2	
M. W.	52	Cyclopal Gr. 10	20	17.2	20.1	85.7	
R. T.	18	Pentobarb. Gr. 13½ (24 hrs.)	40	12.1	18.6	65.2	
M. S.	34	Pentobarb. Gr. 7½ Scopol. Gr. 1/100	60	12.1	15.7	77.2	
S. B.	44	Pentobarb. Gr. 6	30	15.9	21.0	76.1	
D. F.	25	Pentobarb. Gr. 6 Scopol. Gr. 1/100	30	6.2	11.6	53.3	
M. V.	25	Pentobarb. Gr. 4½ Scopol. Gr. 1/100	45	9.9	19.6	50.5	
C. S.	49	Seconal Gr. 6	60	17.3	18.5	93.6	
E. B.	22	Pentobarb. Gr. 6 (3 hrs.)	20	12.6	16.5	76.4	
N. M.	29	Pentobarb. Gr. 6 Scopol. Gr. 1/150	15	13.8	18.9	72.9	48.9
L. H.	22	Pentobarb. Gr. 4½ Scopol. Gr. 1/200	20	11.8	14.5	81.0	
F. M.	24	Pentobarb. Gr. 6 Scopol. Gr. 1/150 M.S. Gr. 1/6	30	14.8	17.2	85.9	
A. T.	28	Pentobarb. Gr. 1½	20	14.7	18.8	78.2	50.0
J. S.	21	Seconal Gr. 4½	30	12.5	15.2	82.6	61.2
U. R.	43	Pentobarb. Gr. 7½ (24 hrs.) Pentobarb. Gr. 6 (11 hrs.) Scopol. Gr. 1/200, 1/200, 1/200	30	12.4	18.0	68.7	
M. D.	24	No sedation	50	15.6	18.7	83.0	76.0
H. V. P.	38	Seconal Gr. 6 (4–6 hrs.) Scopol. Gr. 1/150, 1/150 (3–8 hrs.)	40	11.5	15.5	74.6	52.0
M. M.	28	Pentobarb. Gr. 4½ (1 hr.)	20	16.5	18.3	90.0	64.5
V. D.	20	Pentobarb. Gr. 4½ (7 hrs.) Scopol. Gr. 1/150, 1/150 (5 hrs.)	40	13.7	16.6	82.7	62.3

stagnant and histotoxic factors. Table XV represents arterial bloods on obstetric patients under nitrous oxide anesthesia at the time of delivery (second stage) and the cord blood of the newborn infants. All the mothers had preoperative medication, usually one of the barbiturates with or without scopolamine. The oxygen saturation of the arterial blood was reduced from 0 to 45 per cent, with the greatest reduction found with relatively large doses of pentobarbital and scopolamine. The average reduction in the oxygen saturation of 14.4 is moderate as compared with other groups, but the most significant and dangerous aspect is the irregularity and extreme reduction in seven out of the 20 cases. Raginsky and Bourne,[7] in a series of 14 patients receiving nitrous oxide for extractions and other short operations, found an average reduction in the oxygen saturation of the arterial blood of 25 per cent, but three cases had oxygen saturation of below 55 per cent. The saturation of the cord blood in most instances is well correlated with the mother's arterial blood.

Ethylene was introduced as a clinical anesthetic, in 1923, by Luckhardt and Carter,[22] and Luckhardt and Lewis.[23] Sollmann[15] states that it is an aliphatic narcotic of low activity but with rapid action and recovery. Full anesthesia may be induced with 90 per cent ethylene and 10 per cent oxygen. After induction satisfactory relaxation may be maintained with 80 per cent ethylene and 20 per cent oxygen. It is, therefore, unnecessary to produce anoxia to obtain anesthesia and the color remains good. In the arterial blood of our cases (Table XVI) the oxygen saturation in only one instance was reduced below the level expected in view of the preoperative medication with barbiturates and morphine sulphate.

TABLE XVI

ETHYLENE AND OXYGEN

Patient	Age	Sedation	Duration Min.	Arterial Blood Oxygen		
				Cont.	Cap.	Sat.
S. K.	20	Cyclopal Gr. 10	30	9.2	15.2	60.4%
J. G.	42	Cyclopal Gr. 10	30	13.6	16.0	84.9
A. L.	15	M.S. Gr. 1/6	60	19.1	21.3	89.7
A. H.	22	M.S. Gr. 1/6	60	17.2	19.1	90.2
M. K.	40	Seconal Gr. 6	30	15.4	17.1	90.1
A. K.	39	M.S. Gr. ¼	30	13.9	17.8	78.3
C. P.	62	Cyclopal Gr. 10	30	17.6	19.7	89.0
M. G.	32	Seconal Gr. 6	30	16.4	20.2	81.3
R. E.	40	Nembutal Gr. 6	10	15.7	17.8	87.9
B. R.	59	Nembutal Gr. 6	15	20.0	22.2	90.2

Cyclopropane was proposed as an anesthetic by Lucas and Henderson,[24] in 1929. Since that time, a number of clinical reports indicate its increasing use for induction and more lately from general anesthesia. Sollmann[15] states that 7.4 per cent produces mild anesthesia, 13 per cent is suitable for abdominal operations and 23 per cent is sufficient for deep anesthesia. Any surgical

procedures may, therefore, be undertaken with the patient getting 77 per cent oxygen.

TABLE XVII

CYCLOPROPANE

Patient	Age	Sedation	Duration Min.	Arterial Blood Oxygen Cont.	Cap.	Sat.	Blood Pressure Normal	Anesth.
G. K.....	47	M.S., Gr. 1/6	40	15.8	17.7	89.3%	150/90	110/60
S. V.....	21	Seconal Gr. 4½	15	14.4	16.3	88.2	—	—
M. B.....	44	Seconal Gr. 3	15	21.2	22.1	95.0	120/80	110/76
J. W.....	43	M.S. Gr. 1/6	90	18.5	19.7	92.8	120/80	120/80
M. R.....	33	Seconal Gr. 6	30	10.8	11.5	94.0	150/80	120/80
K. L.....	25	Seconal Gr. 4½	30	16.8	18.8	89.6	118/68	110/70

In Table XVII, the arterial blood oxygen saturation taken during anesthesia shows only slight depression despite the fact that all had preoperative medication with morphine sulphate or seconal. One report of postanesthetic encephalopathy following cyclopropane has been made by Gebauer and Coleman,[25] who conclude that tissue or cellular anoxia is the probable cause of the encephalopathy and death. Their conclusion seems logical, but preoperative medication of sodium amytal 3 gr. and morphine sulphate ¼ gr., the type (thoracoplasty) and length of the operation, and the circulatory depression evidenced by low blood pressure and the rapid pulse should be considered the principal precipitating factors rather than the cyclopropane.

DISCUSSION.—With this study and comparison of the various commonly used narcotics and anesthetics, it becomes apparent that anoxia of some degree and of one or more types usually occurs as a result of their administration. Ordinarily this anoxia is not of sufficient degree to endanger the patient's life or tissues. However, the cases cited here, those of Courville,[1] Löwenberg, Waggoner and Zbinden,[26] Gebauer and Coleman,[25] O'Brien and Steegmann,[27] and Steegmann,[28] doubtless represent only a small percentage of those that will shortly be recorded now that the clinical picture, the pathogenesis and the pathology are identified and are rapidly becoming clarified.

Evipal and the other barbiturates in therapeutic doses produce relatively severe anoxia by respiratory depression (anoxic type), circulatory depression (stagnant type) and reduction of cellular respiration, especially in the brain (histotoxic type). Only the elimination of the barbiturates in large preoperative doses and as anesthetics will prevent anoxia.

Avertin, or tribromethanol, like the barbiturates, depresses both respiration and circulation, resulting in anoxic and stagnant anoxia, but there is relatively little histotoxic anoxia. If measures were taken to combat the early fall in blood pressure and the decreased respiratory rate, the anoxia could be reduced to a minimum.

Spinal anesthesia produces marked circulatory depression through paralysis of the vasoconstrictors in the anesthetized area, leading to stagnant anoxia.

If this vasodilatation and fall in blood pressure is effectively overcome, there is little or no anoxia seen from the spinal anesthesia alone. However, this holds only if the preoperative medication is avoided or kept at minimum levels.

Nitrous oxide-oxygen anesthesia of complete grade requires the reduction of the oxygen in the inspired mixture below maintenance levels (about 6 per cent); therefore, pure nitrous oxide anesthesia predicates anoxic anoxia. It is used only in short anesthesia such as extractions. In longer procedures preoperative medication with barbiturates or morphine sulphate is the rule. Thus both stagnant and histotoxic anoxia are added to make a potentially dangerous total. Apparently little can be done to reduce this risk as preoperative medication is necessary. The nitrous oxide cannot be reduced below the borderline of anoxia, and even with the most cautious administration some of the cases show the arterial blood oxygen saturation at unexpectedly and dangerously low percentages of 50 to 55.

Ethylene and cyclopropane, especially the latter, offer good margins of safety as far as the percentage of oxygen in the inspired mixture is concerned. Anoxia need occur only through heavy preoperative medication or the use of unnecessarily high percentages of the anesthetic gas.

Courville,[1] Löwenberg, Waggoner and Zbinden,[26] and Steegmann[28] have already described the brain pathology occurring after nitrous oxide, avertin and cyclopropane anesthesia. The changes noted by these observers are essentially the same and they correspond closely with those recorded by Gildea and Cobb[29] after experimental ligation of the cerebral vessels, and by one of us[13] following fever therapy with heavy sedation, after large doses of barbiturates, and in acute alcoholism.

The pathologic changes may be roughly grouped into the acute and subacute to chronic. The acute changes may be confined to those in experimental animals or man surviving from a few hours to 24 hours after the production of anoxia. Here marked engorgement of the pial and cerebral vessels is found grossly. The lungs are usually voluminous and of increased density. On section the lung parenchyma is edematous and congested. The other organs show congestion only. Microscopically, the acute changes in the brain are characterized by pericellular and perivascular edema, shrinkage of the pyramidal cells of the cortex and the ganglion cells, and cuff hemorrhages, especially in the basal nuclei. The histologic changes in the lung are typified by the diffuse hemorrhagic infiltration (hemorrhagic pneumonia). At times small hemorrhages may be found in the cortex of the adrenal and in the cortex of the kidney.

In the subacute to chronic cases, that is, in those surviving 24 to 48 hours or longer, all the pathologic changes of the acute phase may be noted in the gross, plus areas of necrosis and hemorrhage. These areas have been called devastation necrosis by Gildea and Cobb[29] and are found most frequently in the basal nuclei. There may be zonal necroses in the cortex, as noted by Courville,[1] or of entire lobes, as noted in the cerebellum of one of our cases.

The changes in individual cells are more advanced, being seen in stages of liquefaction, lipoidal degeneration and calcification.

The lung at this stage either shows resolution of the hemorrhagic lesion of the acute period, or it has gone on to frank consolidation of lobular or lobar distribution. The liver may show central or midzonal necrosis with hemorrhage. The kidney may still show hemorrhage and in addition tubular degeneration.

CONCLUSIONS

(1) Anoxia may usually be demonstrated during anesthesia induced by present-day methods.

(2) Narcotics, particularly morphine and barbiturate derivatives in moderate to large doses, tend to produce anoxia, especially of the histotoxic type.

(3) Destruction of individual cells, vital organs and life itself is most apt to result when a severe histotoxic anoxia is accentuated by one or more of the other types, anoxic, stagnant or anemic anoxia.

(4) Full consideration of anoxia as a source of surgical complications should reduce preoperative narcotics to a minimum, promote the use of anesthetics which allow adequate oxygen in the inspired air, and emphasize the necessity of maintaining the blood pressure and respiration at near normal levels.

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THE PRESENT STATUS OF SPINAL ANESTHESIA*

HAROLD L. FOSS, M.D., AND LEONARD F. BUSH, M.D.
DANVILLE, PA.

FROM THE DEPARTMENT OF SURGERY, THE GEORGE F. GEISINGER MEMORIAL HOSPITAL, DANVILLE, PA.

TO STRICTLY follow the title of this paper would comprehend a survey of the use of spinal anesthesia throughout the civilized world and a summary of the opinions of all surgeons, of the present state of this means of rendering insensibility to pain—obviously an impossibility. One can, however, providing his experience with a method has been sufficiently extensive, arrive at certain conclusions, and, with a survey of a comprehensive literature, state what seems to be the modern evaluation of it. We have, therefore, attempted to sum up present day beliefs regarding an anesthetic technic over which there has probably been more controversy than has occurred in reference to all other anesthetics combined.

In a symposium such as this, in which nearly all modern forms of anesthesia are being considered, spinal as a procedure is of too great importance not to be also represented. Yet, bearing in mind that probably more has been said and written during the past ten years about it than about other methods, one is put to it to approach the subject from an original angle and to escape rehashing what has already been mentioned not once but a thousand times.

Nothing of much value can be added to what has been written with reference to the best drugs to employ and the best technics to be followed in their administration; to the question of indications or contraindications or to that of the selection of the types of patient and operation best suited to the procedure. All these subjects have been extensively dealt with. Much has, however, been contributed lately regarding certain dangers of spinal anesthesia.

Complications of Spinal Anesthesia.—Veal and Van Werden analyzed 30 immediate fatalities in some 33,000 cases in which the method was used in the Charity Hospital of New Orleans. All deaths occurred in the operating room or soon after the injection was made, so there was, in the minds of the authors, no question as to the responsibility of the anesthetic. In the latter half of the series, immediate deaths occurred once in every 1,244 cases. All but four of the deaths occurred with novocain, the authors stating that the risk rapidly rises with the increase of the dosage—yet in 21 of the deaths the dosage was 150 mg. or less.

Davis and Hale Haven carried out injections in dogs. Most marked pathologic change found was meningeal reaction present in a variable degree—an inflammatory reaction in the arachnoid with a thickening of the membrane

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and collections of proliferated arachnoidal cells. Occasionally they found collections of polymorphonuclear cells but in no instance were bacteria discovered. Exudates were largely of the lymphocytic type. In animals killed 30 to 90 days after injection, organization with fibrotic scarring could be seen. The authors conclude that spinal anesthetic solutions are hemolytic as well as myelolytic and that, following injection, there is a varying degree of inflammatory reaction in the leptomeninges. Swelling and pigmentation of the axis-cylinders, occasionally with degenerative changes in the fiber tracts of the cord, occurs. Changes in the ganglion cells of the gray matter similar to those seen in retrograde or wallerian degeneration may frequently be demonstrated but these latter changes are, probably, not of a permanent nature.

Sise, in 1929, collecting the reports of deaths from spinal anesthesia in greater Boston for one year, states that a "rough estimate of the number of spinal anesthetics given during this period forces the conclusion that the death rate has not been better than one to one hundred." Compared with Sise's findings, however, we have the reports of Rygh and Bessesin, analyzing statistics of 250,895 spinal anesthetics with a mortality rate of 1 to 3,345. Obviously such wide discrepancies suggest a lack of standardization in the methods of statistical compilations—a factor which, all too frequently, enters the picture in our scientific investigations, often invalidating the conclusions.

Falk records that in a consecutive series of 260 anesthetics he had no mishap; however, with a change of services three fatalities occurred on the operating table in the next 154 cases—all apparently from acute respiratory failure. A routine dosage of 200 mg. was used in all cases, obviously one far too great.

Many writers have referred to the patient's individual susceptibility and cite, for example, sudden death from nocovain injected into a tonsil. Certain transitory minor effects may well be attributed to a peculiar idiosyncrasy possessed by the patient, or, as has been assumed, to tissue sensitivity to cocaine derivatives.

There is, as pointed out by Harrison, a widespread impression that continued leakage from the puncture occurs and that leakage, by reducing pressure within the subarachnoid space, causes the headache. Introduction of air alone may cause intense headache. Harrison advocates the routine intravenous injection of glucose in the prevention of postoperative spinal headache, the "slight hydremia which the dextrose solution induces being sufficient to check the excessive absorption from the spinal canal—until recovery or until compensation can take place, thereby reducing the disturbance in cerebrospinal hydrostatics to so low a level that the headache does not appear."

Koster *et al.* list the explanations of headache under: (a) Seepage of cerebrospinal fluid; (b) irritative meningitis from the solution from skin contaminations; (c) alterations in the p_H of the solutions. Yet Koster and his associates conclude that any possible contamination from substances used in preparation of the skin plays no part in the production of headache; neither

does the factor of hypo- or hypertonicity. Koster found that the deliberate injection, with the anesthetic agent, of iodine or of trinitrophenol did not increase the incidence of postoperative headaches; neither did the use of tap water or distilled water in the place of saline solution.

Lindemulder concludes that procaine or its allied drugs have a definite toxic effect on the cord and spinal nerve roots which can be shown both clinically and pathologically.

Years ago, Spielmeyer, following injection of stovaine into the subarachnoid spaces of dogs and apes, found degeneration of the roots and the peripheral portions of the cord, and retrograde degeneration in the anterior horn cells. Lindemulder has described degenerative changes in the spinal anesthetics, while Van Lier and Wossidlo demonstrated the toxic effects of anesthetic substances on neural tissues. Lindemulder, Hyslop and Smith have recorded definite instances of neural damage following the administration of spinal anesthetics. Involvement of the cranial nerves is mentioned—abducens palsy seems to be the one most frequently mentioned. Trigeminal, facial and auditory nerve involvements have been referred to.

Kilman and Abbott have found stovaine to cause degeneration of the nerve roots at the periphery of the cord and retrograde changes in the anterior horn cells in dogs and apes. All anesthetics which contained procaine were shown to be myelitic and hemolytic. This was proven by the experimental work on dogs and postmortem examinations on patients who died following the use of spinal anesthesia.

They feel that other factors than the drug may be responsible; inserting the needle too far, after entering the dura; admixture of blood—with resulting fibrosis or leptomeningitis; the needle, striking the anterior wall, injuring veins, and causing bleeding into the cord.

Thompson reports eight fatalities occurring with the use of spinal anesthesia. Seven of these were, possibly, precipitated by the spinal. One patient died suddenly following the administration of the spinal, from no apparent cause other than the anesthetic.

Loeser reports five cases of peripheral neuritis following spinal anesthesia. All patients were discharged well but developed neuritis after long periods.

Anderson reports a case of trophoneurotic gangrene of an extremity following the use of spinal anesthesia, and reviews the literature listing six foreign authors who have described similar cases.

Hyslop, in discussing the nervous system sequelae of spinal anesthesia, stresses the fact that many symptoms may be due to trauma from the needle used. He questions aseptic meningitis or encephalitis as true entities and concludes that there is no evidence to show that cocaine or its derivatives produce permanent central nervous system damage. He does, however, mention the hemolytic and myelolytic actions of the drug.

Koster and Wientrob review 6,000 cases in which spinal was used, with nine deaths which might be attributed to the anesthesia. In none of these

cases did postmortem examination reveal any definite evidence that spinal anesthesia played any part.

Personal Experiences.—The great utility of spinal anesthesia under certain circumstances is recognized by nearly every surgeon. There are still a goodly number of agnostics, but their number is decreasing, about paralleling another phenomenon and one even more fortunate: a decrease in the number who have, heretofore, been unalterable advocates of the method as a routine.

TABLE I

MORTALITY FOLLOWING 10,000 CONSECUTIVE OPERATIONS

(*All Performed on Structures Below the Diaphragm*)

5,000 Consecutive Operations Under Spinal Anesthesia

Deaths	351
Mortality	7.02%
Deaths in operating room	3
Percentage of deaths occurring in operating room to total hospital deaths under spinal	0.88%

5,000 Consecutive Operations Under General Anesthesia

Deaths	255
Mortality	5.1%
Deaths in operating room*	12
Percentage of deaths occurring in operating room to total hospital deaths under general anesthesia	4.7%

* Operating room deaths under general anesthesia show too high a figure—most occurred several years ago, when the anesthetic was straight ether.

(Only two operating room deaths occurred in the last 3,000 operations, all performed under cyclopropane-ether.)

TABLE II

DEATHS IN OPERATING ROOM IN 5,000 CONSECUTIVE OPERATIONS BELOW DIAPHRAGM (SPINAL)

Three Patients Who Died in Operating Room Under Spinal Anesthesia

	Sex	Age	Pathology
1.	F.	52	Supravaginal hysterectomy. Autopsy: (1) Miliary tuberculosis; (2) chronic myocarditis; (3) fatty degeneration of the liver; (4) chronic nephritis; (5) atheroma of the aorta; (6) active pulmonary tuberculosis; (7) active tuberculosis of the spleen
2.	M.	59	Exploratory celiotomy: Carcinoma of stomach with perforating ulcer; peritonitis (lived 15 minutes). No autopsy
3.	M.	35	Exploratory celiotomy: Gastric ulcer (lived 30 minutes). Autopsy: (1) Chronic myocarditis; (2) aortic stenosis; (3) hypertrophy and dilatation of heart

The authors believe that their experience and results have followed fairly closely those of men working in other clinics where spinal anesthesia is extensively used, and so set forth an account of their own conclusions as fairly representative, at least in this country, of the present status of spinal.

TABLE III

OPERATIVE PROCEDURES IN WHICH DEATH OCCURRED

(*Operations All Below Diaphragm*)

	Spinal 5,000 Cases	General 5,000 Cases
Amputations	23	8
Appendicectomies	45	34
Exploratory celiotomies (Chiefly for carcinoma)	53	49
Herniorrhaphies (Strangulated)	28	9
(4 Nonstrangulated)		
Operations upon gallbladder and ducts	52	28
Operations upon kidney, bladder and prostate	32	35
Operations in pelvis	33	24
Operations upon stomach, intestines, *etc.*	81	50
Miscellaneous	4	18
Totals	351	255

TABLE IV

RATIO OF DEATHS FOLLOWING INHALATION ANESTHESIA (5,000) TO THOSE FOLLOWING SPINAL ANESTHESIA (5,000)

	Spinal	General Anesthesia
In operating room	3	13
1st 12 hrs. postoperative	15	26
2nd 12 hrs. postoperative	22	24
3rd 12 hrs. postoperative	34	13
4th 12 hrs. postoperative	26	14
Totals	100	90
After 48 hrs.	251	165
Total deaths	351	255
Mortality*	7.02%	5.1%
Hospital operative mortality as a whole		2.96%

(All were consecutive cases and all operations were performed on structures below the diaphragm.)

* The 2 per cent mortality difference between spinal and ether in the above report is not significant. In a previous study of 2,000 consecutive spinal and 2,000 consecutive general cases, the mortality stood respectively 6.5 per cent and 6.8 per cent. In the last series, the more seriously ill and worst risk cases were handled under spinal, probably accounting for the slightly increased mortality.

Several years ago, the senior author[5] compared the results following the administration of spinal to 2,000 consecutive patients with those following the administration of various forms of inhalation anesthesia to a like number, 4,000 operations in all, performed by himself in the same operating room

and with the same operating room personnel, on structures below the diaphragm. The hospital mortality was found to be equal for the two methods. In the present paper, a series of 5,000 consecutive operations under spinal is taken as a text. All operations were performed by the senior author or by his assistant, in the same operating room, and under like conditions. The patients were followed, during their convalescence, with that degree of care permitted only the surgeon who lives constantly in the institution with his patients, and, therefore, in the closest touch with their progress.

TABLE V

ANALYSIS OF DEATHS IN OPERATING ROOM*

(*5,000 Consecutive General Anesthesias*)

Twelve Patients Who Died in Operating Room Under General Anesthesia

	Sex	Age	Operative Procedure
1.	F.	35	Suturing traumatic rupture of the uterus; advanced peritonitis
2.	F.	29	Salpingo-oophorectomy; cardiorespiratory failure
3.	F.	66	Appendicectomy; gangrenous appendicitis; cardiorespiratory failure; peritonitis
4.	M.	60	Exploratory celiotomy (chronic cholecystitis and pancreatitis); chronic myocarditis; cardiac failure
5.	M.	62	Closure—perforated duodenal ulcer; generalized peritonitis
6.	F.	26	Exploration—retroperitoneal sarcoma; cardiorespiratory failure
7.	M.	36	Secondary, exploratory celiotomy; hemorrhage following gastro-enterostomy performed 17 days previously
8.	F.	29	Salpingectomy, ectopic pregnancy; extensive preoperative hemorrhage
9.	M.	60	Died of intestinal obstruction before incision could be made
10.	M.	15	Open reduction and plating; fracture of the femur; cardiorespiratory failure
11.	F.	27	Cesarean section (prolonged labor with exhaustion and toxic contracture of uterus)
12.	M.	29	Amputation of toe (diabetic gangrene of toe with cellulitis of foot)

* Most occurred several years ago—and under straight ether. But two operating room deaths occurred in the last 3,000 operations under general anesthesia—all under cyclopropane-ether.

The advantages of spinal anesthesia, the ease with which it may be administered, the almost complete relaxation it produces and the generally satisfactory postoperative results have received widespread acceptance. However, that the method is not free of danger and, at times, is followed by serious complications, is also realized. The occasional appearance of alarming and unexpected sequelae in the human, and the easy confidence with which the procedure is condemned by certain laboratory workers, whose researches upon animals lead them to conclude that serious changes in the meninges and cord all too frequently occur, have caused the method to be the subject of severe and widespread criticism. It is with this especially in mind that the authors have reviewed their own personal experiences and have examined them in the light of what has been recently written on the dangers, complications, untoward results, *etc.*, of spinal anesthesia.

We have long known that spinal anesthesia should never be a method to

employ routinely. Neither should any other single form of anesthesia, for that matter; also, we have realized, as have most surgeons, that the method is most applicable in operations below the diaphragm—better, below the level of the umbilicus—and we have appreciated that there are definite contraindications to the method and that, while there are many technics being employed, there are but one or two that are best.

In evaluating the comparative safety of an anesthetic, we have no recourse but to compare it with open drop ether or gas-ether, quite universally considered the safest of all anesthetic methods. This plan we have followed, especially in reference to operating room deaths, deaths in the first four days in 12-hour groups and, finally, hospital deaths.

TABLE VI

RESULTS OF QUESTIONNAIRE TO POSTSPINAL PATIENTS

(*1,175 Letters. 911 Replies*)

(1) Have you ever had ether or gas anesthesia before having spinal?

Yes—391
No —520

(2) If you were operated upon again, would you choose spinal?

Yes—736—80.7%
No —137—15.0%
Undecided—38

Next the question of postoperative morbidity, of hospital and posthospital complications of a temporary or permanent nature, has been considered. Here one runs into a difficulty for, with the exception of certain respiratory complications which are now considered to be no less common after spinal than after inhalation anesthesia, surgeons do not commonly think of serious complications attributable to inhalation anesthesia. While in the consideration of postoperative mishaps, inhalation anesthesia usually goes scot free, there have, however, been endless reports of temporary or permanent complications following the injection of various anesthetic drugs into the subarachnoid space.

It is hardly fair, however, to consider inhalation anesthesia as completely free of danger. The safety of open drop ether has been axiomatic—its dependability and freedom from unexpected untoward effects have rendered it proverbially a safe anesthetic equaled only by some of the newer gases, especially ethylene and cyclopropane. It has, however, been disheartening to recently learn that these two anesthetics, first ethylene and now, more recently, cyclopropane, possess smoldering properties of terrifying power which are capable of being unloosed unexpectedly and with fearful and often tragic results. Over 150 explosions of gas or gas-ether mixtures, 79 of which have been carefully investigated, and in which 22 persons have lost their lives, have occurred during the past few years. These unfortunate occurrences have boosted the stock of other anesthetics, ether again, and with it spinal. As the latter had a reputation by no means devoid of obliquity, it

has greatly needed some revivifying from the low estate into which it has sometimes fallen. The unexpected and unpredictable reactions it may produce, even resulting in sudden death from acute respiratory paralysis, and especially the late neuromuscular complications which may follow its administration have all freely been broadcast and much to its detriment.

TABLE VII

QUESTIONNAIRE TO POSTSPINAL PATIENTS

Did you ever have ether or gas anesthesia before this operation?

Yes—215
No —290

Of the 215 patients who had both spinal and general anesthesia, 154 would choose spinal were they to be operated upon for a third time, or approximately 72 per cent.

QUESTIONNAIRE TO PATIENTS HAVING AN ANESTHESIA (SPINAL) FOR THE FIRST TIME

Would you choose spinal anesthesia if you were operated upon again?

Yes—416
Undecided—15
(depending on operation)
No — 89

Of 505 patients answering questionnaire, 82.3 per cent would choose spinal for their next operation were it advisable.

We have in our own clinic, for years, been on the watch for these untoward conditions. While headaches have occurred, but with decreasing frequency, we have never seen in the hospital a single example of serious cord or meningeal injury. Foot drop, which has often been referred to as a common result of intraspinal injections, we have never seen. Neither have we ever had a patient who, before leaving the institution, has called our attention to impairment of motor function, to interference with the anal or vesicle sphincter control, to anesthesias, or paresthesias, or other evidences of definite nerve damage. We have never seen paralysis, either complete or partial, and certainly never the appearance of decubitus ulcers, retention of urine and feces or symmetric muscular atrophy, frequently referred to.

Occasionally, and usually months after the patient's discharge, either directly or otherwise, word has come to us of his complaining of persistent pain in the back, of vague numbness in the lower extremities, or, very unusually, of persistent headache. These reports have prompted further efforts toward investigating, by direct communication with the patient and, when feasible, by an office examination, to what degree actual nerve damage had occurred. Furthermore, to determine how great the incidence of late complications has been, 50 letters were sent to physicians who regularly refer the largest number of patients to us for surgical treatment, as well as 1,000 letters to patients upon whom we had operated upon under spinal anesthesia one year or more before.

It is interesting to note that in following the patients who reported postoperative complains, most were found to have symptoms in no manner related to the anesthetic. For example, one patient emphatically denounced spinal anesthesia because of numbness in her legs and progressive loss of motor function in the lower extremities. The patient had had a plastic operation performed for cystocele and rectocele under spinal anesthesia. Some months later, she reentered the hospital complaining of the loss of strength and leg weakness, firmly believing it to be due to spinal anesthetic. Subsequent studies showed that she had rapidly progressing pernicious anemia with associated cord changes. However, this patient is not convinced that it was not the spinal that accounted for her trouble and, as her story has become well known, it is rare that a patient comes from her community but refuses to have spinal administered. Similar situations have arisen in other communities where spinal anesthesia has become widely condemned because of postoperative complications, imagined or otherwise, and yet in no possible way the result of the procedure. One patient, who has an advanced chronic polyarthritis, attributes her trouble to a spinal anesthetic administered some years ago; while still another, returning for examination in answer to our questionnaire and complaining of pain in her legs, was found to have cardiac decompensation with edema and extensive phlebitis.

In reviewing the literature dealing with postspinal injection complications, we have been impressed by the fact that in many instances, if not in the majority, untoward effects have appeared following the injection of drugs administered in combination, and that the complications seem to be of a lower incidence when procaine alone has been used. We are not convinced of the utility or safety of injecting with the anesthetic, strychnine, alcohol, starch or any of a dozen accessory substances so frequently hailed as valuable adjuncts.

We are amazed at the high incidence of serious postoperative effects which have been referred to by certain surgeons who have been led, from their unfortunate experiences, to urge that spinal anesthesia be restricted to a special group of patients or, perhaps, never to be used at all. We would long since have turned away from spinal anesthesia had we, if but occasionally, had the harrowing experience of seeing our patients develop meningitis, "aseptic" or otherwise, cauda equina neuritis, transverse myelitis, or lumbar radiculitis, as mentioned by Brock and his associates.

It is probably true that many writers, particularly those speaking in enthusiastic advocacy of spinal, frequently are unaware of and, therefore, omit reference to nervous system injury, yet we repeat that with an open-minded approach to the subject and after a careful watch over a period of many years, we have not discovered prominent or even mild complications in our patients which would lead us to consider spinal a procedure possessing dangers outnumbering those commonly ascribed to other popular forms of anesthesia.

Toxic myelopathy, extensive destruction of the myelin sheath, axis-cylinders and glia, mostly at the periphery of the cord and at the zones of en-

trance of the posterior roots, have been the chief findings at postmortem examinations of patients dying from cord lesions (Brock), following subarachnoid injection of cocaine derivatives. Changes in the ganglion cells of the anterior and lateral horns have been found in toxic and experimental myelopathy induced by various spinal anesthetics.

No doubt, if it were possible for every patient, during the postoperative course, to have a careful neurologic examination by an unbiased and skilled examiner, much evidence, not obvious to the surgeon, indicating at least transitory irritation of the cord or its membranes would be discovered in every clinic where spinal is used. And this applies to our own. Nevertheless, in its daily use over a period of ten years in thousands of cases we do not recall a single incident in which the patient complained of symptoms of any consequence and which could be blamed on the method, or do we recall any patient whose convalescence was prolonged by a postspinal complication.

Of 515 consecutive patients having had spinal, who replied to a questionnaire, 130 had transitory headaches, while 375 had none. Of the 130 having had it, 69, or 53 per cent, were subject to it anyway. One hundred thirty-seven reported they experienced some postoperative numbness or pain, while 368 experienced no such discomfort whatever. Of the 137 having trouble, 66 experienced it but a few hours. Of the 137, 74 stated they would choose spinal if they had to be operated upon again. To the question "Did you have any other unpleasant reactions?" 70 replied yes, while 435 replied in the negative. Of the 70, 54 mentioned as their chief complaint backache of varying degrees and remaining present for from one week to several months. The majority, complaining of backache, stated that the pain occurred near the surface and at the point where the needle had been inserted. Of the relatively few patients who reported remote complaints, more, by far, referred to backache than to any other symptom.

Among the 5,000 consecutive operations under spinal, all performed below the diaphragm, there have been three deaths in the operating room, one in the first 2,000 and two in the remaining 3,000.

Of the two patients dying in the latter 3,000, one was a male, age 59, operated upon for a ruptured, carcinomatous ulcer of the pylorus, with peritonitis, who died 15 minutes following the administration of 120 mg. of neocaine. No autopsy was obtained.

The second was a male, age 34, who died 30 minutes following the administration of 200 mg. of novocain, the operation being an exploratory celiotomy for gastric ulcer. Autopsy revealed a chronic myocarditis and chronic endocarditis with aortic stenosis, cardiac hypertrophy with dilatation. From the pathologist's findings it was obvious that the patient might have as promptly succumbed under a general anesthetic.

While among our last 3,000 patients operated upon under spinal, there were two deaths in the operating room, at the same time, with a consecutive series of 3,000 patients operated upon for lesions below the diaphragm, and under general anesthesia, there were also two operating room deaths.

A questionnaire was sent to the 50 doctors who refer us the greatest number of patients. Thirty-six responded, 31 of whom stated that they have had no complaints from their patients. Five doctors returned the questionnaire giving the names of six patients who had postoperative symptoms. Five of these have been examined with the following results.

One, who complained of pain in her left leg, has chronic phlebitis.

One, who complained of headache for two weeks after operation and which cleared up spontaneously.

One, who complained of girdle pain, has developed a small recurrent incisional hernia. She weighs 250 pounds, is definitely hypothyroid and is being treated.

One complained of pain and weakness in her ankles. These have been swelling for eight years. She has shortness of breath. On examination she was found to have a systolic murmur, marked varicose veins, and pitting edema of both ankles. She was placed on medical treatment and her symptoms are improving.

One, a woman, age 48, complained of severe girdle pains and pains in her extremities. Check-up examination showed her to be suffering from a chronic polyarthritis with marked deformities of all the joints of her hands and feet. Roentgenologic examination revealed marked spondylitis of the lumbar vertebrae.

All of these patients from whom complaints were received were women, well beyond middle age. In all instances, we found that spinal anesthesia had nothing whatever to do with their present symptoms.

CONCLUSIONS

(1) Spinal anesthesia, as a method of rendering insensibility of pain, is of the very greatest utility.

(2) It is a safe procedure, as anesthesias go, and when measured in a comparative study of 10,000 operations performed by the same surgeon, was found to equal the safety of general.

(3) The likelihood of operating room deaths is no greater with spinal than with general anesthesia.

(4) With proper technic, the likelihood of serious nerve and meningeal damage is infinitesimal.

(5) Most abdominal operations are greatly facilitated by this method. For certain ones, it is almost impossible to operate without it.

(6) In many operations extensive trauma under general anesthesia is inevitable. In such instances the risk of spinal, if any exists, is more than offset by the decreased risk resulting from the lessened visceral trauma made possible by the more complete relaxation.

(7) Spinal is a procedure against which there has been a great deal of criticism, based largely upon bad results following poor selection of patients, and, especially, following improper technic. The method is one not for routine application and, when used, must be *skillfully* administered,

(8) It is quite probable that other drugs of lesser toxicity, and of even greater potency, will yet be synthesized, ultimately rendering spinal anesthesia, especially in major surgical operations below the diaphragm, the most generally satisfactory, indeed the safest, of all known forms of anesthesia. Indeed, it is not far from that status now.

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SPINAL ANESTHESIA IN ABDOMINAL SURGERY*

ROSCOE R. GRAHAM, M.B., AND W. EASSON BROWN, M.B.
TORONTO, CANADA

SPINAL ANESTHESIA has been developed to a degree which has proved its usefulness. The conflicting opinions expressed regarding this means of inducing anesthesia seem irreconcilable. The fact that such a variety of anesthetic drugs is employed indicates either the inadequacy of these drugs, or an incorrect method of administration. The undesirable sequelae reported would seem sufficient to utterly condemn the procedure. The amount of scientific nonsense which has been broadcast in respect to spinal anesthesia is amazing. On careful enquiry, many statements condemning the procedure are based on hearsay unsupported by scientific facts. An analysis of many of the reported shortcomings will reveal the fact that the anesthetic was not administered and supervised by a competent anesthetist. We cannot too strongly condemn the surgeon who gives his own spinal anesthetic and leaves the supervision of the anesthesia to an indifferent associate.

A death during or immediately following an ether anesthesia, because of the supposed safety of this anesthetic agent, is accepted as inevitable, and soon forgotten. The slightest discomfort or unusual happening following an operation performed under spinal anesthesia is often attributed, unquestionably, to the spinal anesthetic, with no attempt to support such condemnation by facts.

To assess properly the value of an anesthetic agent, one must take cognizance of not only the patient's condition during the operation, but also during the convalescence. The ideal anesthetic must achieve:

(1) Safety.
(2) Freedom from discomfort during administration.
(3) Abolition of pain and muscle spasm of sufficient duration to carry out prolonged and complicated operative procedures.
(4) A state of relaxation which permits careful and accurate dissection without traumatic retraction.
(5) Freedom from postoperative sequelae.

No single anesthetic agent, so far evolved, can fulfill all these conditions. Under certain conditions spinal anesthesia fulfills these requirements to a greater degree than other anesthetic agents either singly or in combination.

Where is spinal anesthesia of the greatest value? While it has been used extensively by Shenstone and Janes[1] in thoracic surgical procedures, it is in operations within the peritoneal cavity where it has contributed so much to the advantage of the patient. This is particularly true where the surgical procedure is carried out in the upper abdomen or on the colon or rectum.

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The ability to carry out a careful atraumatic operative dissection in a difficult upper abdominal lesion reflects an advantage to the patient in several ways. An adequate operation can be carried out, thus ensuring to the greatest degree freedom from future trouble. Primary healing with a minimum of wound reaction takes place. Lesions, questionably operable with inhalation anesthesia, can often be dealt with effectively. This is particularly true of a high-lying gastric ulcer or gastric cancer. Because of the ease and safety of exposure of the common bile duct with spinal anesthesia, in a study of the last 311 cases, we explored the common bile duct in 46.9 per cent, and in the cases of calculous cholecystitis removed stones from the common bile duct in 21.4 per cent. This is at variance with our experience in biliary surgery under inhalation anesthesia, when, because of technical difficulties, largely the result of inadequate exposure, exploration of the common bile duct added greatly to the operative mortality, and hence such exploration was only undertaken when it was obvious that a stone was present. The number of common duct stones that were overlooked is only now becoming apparent. Should not such increased mortality and morbidity properly be assesed as due to the inadequacy of inhalation anesthesia, rather than to the inadequacy of technical surgical skill in the face of a serious pathologic lesion? As the result of an analysis of the last 511 operations upon the biliary tract carried out under spinal anesthesia, we now may open the common duct whenever our judgment suggests such is wise, having satisfied ourselves that this procedure will not increase either the mortality or the morbidity of the operative procedure.

The gentleness with which a perforated duodenal ulcer is exposed while tying a fat graft in place to close the perforation[2] is of the utmost importance in decreasing the mortality from this lesion. Spinal anesthesia achieves this. Further, the vigorous respiratory efforts associated with the induction of inhalation anesthesia are a great factor in disseminating the gastroduodenal contents which have been expelled through the perforation. Spinal anesthesia eliminates this. The routine use of spinal anesthesia in patients suffering from an acute perforation of a duodenal ulcer has in no small measure contributed to the recovery of 72 out of 76 such patients consecutively admitted to and operated upon by the staff of the First Surgical Division of the Toronto General Hospital. However, such advantages avail little unless accompanied by immediate safety and an absence of disastrous sequelae.

Our observations are based on an experience with 13,136 spinal anesthesias carried out by the Anesthetic Staff of the Toronto General Hospital, between January 1, 1930, and January 1, 1939. We have also made an analysis of 1,918 cases upon which one of us has operated, in which there were 202 hospital deaths. The analysis reveals a death rate of 10.4 per cent in this group of cases operated upon under spinal anesthesia. When one realizes that included in this group are the cases of serious and advanced malignancy, as well as the cases of acute intestinal obstruction, this mor-

tality is not forbidding. The operative mortality of one of us has ranged from 1.1 to 6.4 per cent per annum over the nine-year period, averaging 4.1 per cent. In view of the fact that we have been carrying out, whenever possible, palliative resections in the advanced cases of gastro-intestinal malignancy during this period, it impresses us that spinal anesthesia has in no small degree contributed to this low operative mortality.

A critical analysis of the 202 deaths in patients operated on under spinal anesthesia reveals three deaths which occurred on the table and two shortly after return to the ward, which might be contributed to by the anesthetic. An analysis of these cases follows:

ANALYSIS OF FIVE PATIENTS DYING AFTER SPINAL ANESTHESIA

Case 1.—H. R., male, age 52, weight 270 pounds. Operation upon biliary tract. Spinal anesthetic: Novocain crystals, 400 mg. dissolved in 10 cc. of spinal fluid injected at the level of lumbar IV to V at the rate of one cubic centimeter every four seconds. When peritoneal cavity was opened, respirations ceased suddenly. At autopsy, fatty degeneration of heart and liver. In absence of any other satisfactory explanation, death is attributed to the anesthetic, with the suggestion that despite his weight of 270 pounds, 400 mg. of novocain crystals was probably an excessive dose.

Case 2.—W. S. A., male, age 71. Perforated duodenal ulcer. Spinal anesthetic: novocain crystals, 200 mg., dissolved in nine cubic centimeters of spinal fluid, injected at the rate of one cubic centimeter every three seconds. As the abdomen was opened and the ulcer visualized, he died suddenly. No autopsy was obtained. He had previous severe cardiovascular disease, and one suspects a cardiovascular accident, but in the absence of an autopsy we must attribute death to the anesthetic.

Case 3.—F. W., male, age 68. Jaundiced; stone in the common bile duct. Spinal anesthetic: Nupercaine 1 in 1,500 dilution. Eighteen cubic centimeters injected between third and fourth lumbar vertebrae, taking 15 seconds for the injection. One and one-half hours after the administration of the anesthetic, systolic pressure fell; respirations ceased. Heart continued to beat for a few minutes. Autopsy revealed massive bilateral pulmonary collapse, with no obvious explanation; hence death attributed to anesthetic.

Case 4.—W. J. H., male, age 71. Abdominoperineal excision of the rectum. Spinal anesthesia: Nupercaine, 17 cc. of 1 in 1,500 dilution, injected between the second and third lumbar vertebrae. On return to bed, sudden unconsciousness, cyanosed, gasping respirations; death in few minutes. We suspected a cardiovascular accident, but were unable to secure an autopsy to support this; hence attribute death to anesthetic.

Case 5.—J. R., male, age 54. Recurring jejunal ulcer. Spinal anesthesia: Nupercaine, 17 cc. of 1 in 1,500 dilution, injected. Was given, during the operation, a sedative in the form of two intravenous injections of sodium amytal, the first injection being three grains and the second four grains. This was followed by supplementary deep ether anesthesia. Returned to bed, but had respiratory difficulty, was cyanosed, and never regained consciousness. At autopsy, no obvious cause of death found. It is presumed that the anoxia from which he suffered during the induction of his ether anesthesia produced cerebral damage which resulted in his death.

In Case 4 it is suggested that the change to the jack-knife position for the perineal stage was a contributing factor to the patient's death. The systolic pressure fell at this time. The further change of position on returning the patient to bed was accompanied by a further disturbance of circulation. This experience has led us to carry out the second stage of an

abdominoperineal resection of the rectum with the patient in the left lateral position. This we find is accompanied by much less cardiovascular upset.

In Case 5, because of restlessness, sodium amytal was given intravenously during the operative procedure, on two occasions, a total of seven grains being administered. It was then necessary to give supplemental inhalation anesthesia. Open ether was used. This was very difficult because the heavy sedation produced depressed respiration. It is suggested that the associated anoxia produced sufficient cerebral damage to explain the fatality.

During 1938, on the University Surgical Service of the Toronto General Hospital, a careful record was kept of all the sequelae which followed upper abdominal operations. During this period many of the anesthetics were given by interns of varying ability. For this reason, in many cases where spinal anesthesia was used, relatively large bore needles of No. 19- or 20-gauge were used for the spinal puncture. The foot of the bed was not elevated when the patient was returned to the ward.

The series includes 93 operations upon the biliary tract, 49 gastric resections, 11 perforated ulcers of the stomach or duodenum and five miscellaneous operations, a total of 158 operations, 144 of which were carried out under spinal anesthesia. This most eloquently expresses the preference of the Staff for spinal anesthesia in the major upper abdominal operations. In Table I are detailed the character and incidence of the postoperative sequelae following these operations.

TABLE I

POSTOPERATIVE SEQUELAE FOLLOWING 144 SPINAL ANESTHESIAS

Pulmonary collapse, even minor degree	15 %
Pneumonia	4 %
Headache	3.7%
Urinary retention less than 24 hrs.	10.1%
Urinary retention longer than 24 hrs.	8.2%
Abdominal distention, even minor degree	19 %
Deaths in hospital	10.1%

The 10.1 per cent mortality in this group on the University Service is practically the same as for the same group of private patients. Of the 144 patients who were operated upon under spinal anesthesia, 14 died. A careful analysis of these deaths fails to include, in any instance, the spinal anesthetic as a contributing factor in the patient's death. The shortest interval between operation and death was three days. Eight died of peritonitis; two of pulmonary emboli; one of coronary thrombosis; two of pneumonia and one of cholangitis. There has not been a single tragedy as a sequelae. The only nerve lesion was a paresis of the left third nerve, which cleared up in less than three weeks. The anesthetic staff have no explanation of this occurrence. It was not accompanied by any other unusual occurrence. It was discovered the day following operation, and is thus attributed, rightly or wrongly, to the spinal anesthetic.

The necessity for catheterizing the patients postoperatively is more fre-

quent than after inhalation anesthesia. While the incidence of chest complications is approximately the same as after inhalation anesthesia, the serious lesions are less frequent, and fatalities from respiratory infection are infrequent. Many cases diagnosed as dying from pneumonia postoperatively are found to have a fatal peritonitis at autopsy. The aspiration of the bronchi by a urethral catheter, as advocated by John Alexander,[4] of Ann Arbor, has proven of great advantage in the cases with pulmonary collapse. The volume of mucus which it is possible to aspirate by this procedure is surprising.

Despite these sequelae, the benefits of the anesthesia in our opinion outweigh the disadvantages, and indeed, apart from the necessity of more frequent postoperative catheterization, we believe the sequelae are no more than those following inhalation anesthesia with ether.

Why, then, is there such a conflict of opinion regarding the value of spinal anesthesia? This we believe results from two sources: First, the character of the drug used; and second, the experience of the anesthetist. The drugs used for inducing anesthesia are either: (A) Isotonic with the spinal fluid. (B) Heavier than the spinal fluid. (C) Lighter than the spinal fluid.

When a drug is used in which the level of anesthesia is determined only by elevation or depression of the patient's torso, we believe the factor of error and the possibility of accident are too great to warrant its use. For this reason we have never used such agents, of which spinocaine, and more recently pontocaine and glucose, are the most popular. We prefer to use as anesthetic agents those in which the height of anesthesia is determined by the volume of fluid injected into the spinal canal. The natural curve of the spinal column is utilized as a protection against respiratory paralysis which results if the anesthetic reaches the cervical region. The drugs we use are procaine and nupercaine. The former is used if the operation will be of less than one hour's duration, or in the cases where it is impossible for the patient to lie on the abdomen, as is necessary if nupercaine is used. This latter drug almost invariably will give adequate anesthesia for at least two hours. In our experience there is less fall of the systolic blood pressure with nupercaine than with procaine, although with expert supervision this disturbance may be controlled adequately in most instances.

The second factor which has led to the condemnation of spinal anesthesia is an erroneous method of administration. We cannot too strongly condemn the practice of a surgeon being his own anesthetist. The technic of administering the anesthetic is important, but of no more importance than the preparation of the patient for the anesthetic, or the intelligent supervision of the patient throughout the whole operative procedure. Spinal anesthesia is a dangerous anesthetic agent unless administered and supervised by an expert anesthetist trained in spinal anesthesia.

With the exception of the increased incidence of postoperative catheterization, the complications seen on the University Service are conspicuous by their absence. On the private side particularly, is this true of headache and

abdominal distention. Headache now is a rarity following spinal anesthesia. In the clean abdominal cases, postoperative distention as a complication is infrequent, much different from our experience with the same type of case when the operation was carried out under inhalation anesthesia. This freedom on the private side from postoperative complications after spinal anesthesia can be due only to the fact that in each instance the patient is prepared, anesthetized and supervised by an expert medical anesthetist. This we believe to be of the utmost importance, if we are to secure the greatest advantages from the use of spinal anesthesia.

The following is the technic which we have come to adopt. We shall discuss the four stages which we believe to be important:

(A) *Selection of the Patient.*—With increasing experience, we have extended the use of spinal anesthesia very greatly. Emergency operations have been necessary when we felt it wise to modify our previously determined contraindications and use spinal anesthesia, and to our delight the patient benefited. As a result of such experience we have gradually decreased our contraindications. In the elderly patient, with severe cardiovascular disease associated with hypertension, or a history of previous vascular accidents, spinal anesthesia is given only if the disease be of a lethal character and when perfect relaxation permitting meticulous atraumatic dissection is essential to recovery. We gradually are being convinced that with adequate collateral support few patients need be denied the advantages of spinal anesthesia. In patients with carcinoma of the stomach or colon, adequate contraindications must be advanced to deny such patients a spinal anesthetic. We believe, in diseases of such seriousness, such contraindications must be extremely rare. A surgeon who operates upon a patient suffering with acute intestinal obstruction using inhalation anesthesia, if adequate facilities for spinal anesthesia are available, is guilty of malpractice. In the presence of an acute intraperitoneal inflammatory lesion, such as a perforated ulcer or a perforated appendicitis, the advantages of the "still" peritoneal cavity accompanying spinal anesthesia are obvious.

(B) *Preparation of the Patient.*—The adequate restoration of body fluids and salts should be always assured before anesthesia. This may be accomplished by the oral or intravenous administration of fluids. Blood transfusion is of great help on occasions. So much importance do we place on the correction of the biochemical upset, that we will defer operation for some hours, even when the diagnosis be that of a perforated duodenal ulcer. To administer a spinal anesthetic to a dehydrated or exsanguinated patient, is to court disasters which cannot properly be charged to the anesthetic procedure, but to poor judgment and inadequate knowledge of the collateral disturbances which accompany such states.

Adequate preoperative sedation is of the utmost importance. The variable definition of "adequate" explains further conflict of opinion regarding the merits or demerits of this anesthetic procedure. If we achieve for the patient a drowsiness which is accompanied by an utter disregard for the

surroundings, we believe we have adequate sedation. Anything short of this is inadequate. With inadequate sedation we have an apprehensive patient, with all the associated physiologic and biochemical phenomena. Most important from our standpoint are an acceleration of the pulse and increased respiratory rate. Nausea during the operation is very rare in the presence of adequate sedation. To achieve adequate sedation, the following medication is administered: Starting 1½ hours preoperative, we give to adult patients morphia Gr. ¼, hyoscine Gr. 1/200. Three-quarters of an hour preoperative, we give morphia Gr. 1/6, hyoscine Gr. 1/400 (in female patients morphia Gr. ⅛). One hour preoperative, nembutal Gr. 1½ per os—this repeated in 20 minutes if patient not dozing, and if alert on reaching the operating theater, a further Gr. 1½ is repeated. This latter dose of nembutal is rarely necessary. If, after the anesthetic is administered, the patient is still wakeful or nauseated, sodium amytal is administered intravenously. If intravenous fluid is being administered, the sodium amytal is given slowly into the intravenous tubing until the patient becomes quiet. Usually about two grains will suffice and often no more is required. If after some time the patient shows signs of restlessnes, further administration of approximately one grain may be administered, the patient's quietness being the criterion of dosage. If, however, the duration of the operative procedure is such that there is a possibility of supplementary inhalation anesthesia being necessary, all intravenous sedation should be withheld and inhalation anesthesia given in its place, the agent used being either nitrous oxide, cyclopropane or a combination of either with ether. The difficulty and danger of administering supplementary anesthesia with heavy sedation is too obvious to require discussion. For this reason, if supplementary anesthesia is necessary in an upper abdominal operation, we use splanchnic anesthesia and field block of the abdominal wall. The technic popularized by Finsterer, of Vienna, we have found adequate and of great advantage. By such we avoid the necessity for deep inhalation narcosis.

(C) *Technic of Administering the Anesthetic.*—Before the anesthetic is administered, a hypodermic injection of Gr. ¾ of ephedrin is given: the patient lies on the side with the knees drawn well up and the back bowed with the assistance of a nurse. A midline puncture of the spinal canal is made with a sharp short-beveled No. 22-gauge needle. We are convinced of the value of the small gauge needle. The level and duration of anesthesia is determined by the volume injected. With nupercaine we always use a solution of 1-1,500 dilution, and in a difficult and complicated gastric case have injected as much as 19 cc. without the withdrawal of spinal fluid. The nupercaine solution is injected quite slowly, so that undue pressure will not occur in the spinal canal. The patient is then made to lie on the abdomen for eight to ten minutes. This step of course is unnecessary if procaine is used. It is of the utmost importance to make sure that with the patient lying on the abdomen, the upper thoracic curve of the spinal column is higher than the cervical region. A pillow placed under the chest while the patient

lies on the abdomen ensures this and prevents the anesthetic agent from going too high. It is quite unnecessary to tip the table. If the operation be of lesser magnitude, or if for some reason the patient cannot lie on the abdomen, procaine in crystal form is substituted for nupercaine. The maximum dose should not exceed 300 mg. and is dissolved in the withdrawn spinal fluid. Twelve cubic centimeters volume will ensure anesthesia in the upper abdomen. During the operative procedure a tent is made over the patient's head by using the end of the laparotomy sheet and a stream of oxygen is run in at the rate of 60 liters per hour. Ravdin[5] has recently supported the wisdom of this procedure. During the operation, observation of the blood pressure and pulse rate are made at five to ten minute intervals, and any tendency to a fall in the systolic blood pressure is combated by the repeated injections of small doses of epinine combined with ephedrin during the operation. Usually about three minims of epinine and Gr. ¼ of ephedrin is given at one dose. This type of supervision enables the anesthetist also to anticipate the necessity for the intravenous administration of fluids before an acute emergency arises.

(D) *Postoperative Precautions.*—When the patient is returned to bed, an intravenous of at least 1,500 cc. of normal saline is administered by the drip method at a rate of approximately 125 cc. per hour. The foot of the bed is elevated six inches for ten hours. To these two procedures, and the use of No. 22-gauge needle for introducing the anesthetic agent, goes the credit for the almost complete disappearance of "spinal headache" in the private cases. Over-breathing of the patient stimulated by the administration of carbon dioxide, together with a change in position of the patient from one side to the other every two hours for the first 24 hours after operation, does much to minimize the respiratory complications. If signs of pulmonary collapse, such as dulness on percussion and fine râles are heard, the suggestion of Dr. John Alexander[4] to aspirate the bronchus with an urethral catheter has been of great help, and the simplicity and ease of its execution commends itself to us. If the patient has not voided in 12 to 14 hours postoperatively, an urethral catheter should be passed. This may have to be repeated, but we have had no case when this complication, if such it be, was more than a nuisance.

CONCLUSIONS

(1) The evolution of spinal anesthesia has reached a stage where the permanence of the procedure is assured.

(2) Its safety is in direct ratio to the experience of the anesthetist. It must be administered and supervised during the operation by a physician specially trained in its use.

(3) Nupercaine in dilution of 1:1,500 is the agent of choice, being replaced by procaine when conditions prevent its use.

(4) Adequate preoperative sedation is of great value during the opera-

tion in preventing nausea and the acceleration of the pulse and respiratory rate, as well as lessening the changes in the blood pressure.

(5) A gross fall in the systolic blood pressure can be prevented by the hypodermic injection of Gr. ¾ of ephedrin immediately before administering the anesthetic and the injection of small doses of epinine and ephedrin during the operation whenever any fall in pressure commences, further controls serious fluctuation of the systolic pressure.

(6) Anoxia is prevented by a stream of oxygen run into a tent about the head, formed from the end of the laparotomy sheet.

(7) The use of a small No. 22-gauge needle for the spinal puncture reduces to a minimum the leak of spinal fluid from the dural puncture. The prevention of such a leak in conjunction with the intravenous administration of fluids by the drip method and elevation of the foot of the bed immediately following the operation has practically eliminated the "spinal headache."

(8) Postoperative over-breathing, stimulated by the administration of carbon dioxide, together with frequent changes in posture, minimize the incidence and seriousness of chest complications.

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FURTHER EXPERIENCES IN THE USE OF SPINAL ANESTHESIA FOR THORACOPLASTY*

FRASER B. GURD, M.D., A. M. VINEBERG, M.D., AND WESLEY BOURNE, M.D.

MONTREAL, CANADA

FROM THE GRACE DART HOME HOSPITAL (FOR PULMONARY TUBERCULOSIS), MONTREAL, CANADA

IN JUNE, 1937, a paper[1] describing our experiences in the employment of spinal anesthesia for thoracoplasty was read before the American Association for Thoracic Surgery. At that time, we reported that, commencing in July, 1936, we had operated upon nine patients and performed 17 operations for thoracoplasty under spinal anesthesia. We now feel it advisable to report our experiences since that date.

Sixty-seven cases of extrapleural thoracoplasty (including five cases of extrapleural pneumothorax induction) have been operated upon at the Grace Dart Home Hospital since 1934. The clinic is not a large one, and during the two years from July, 1934, to July, 1936, 27 cases have been operated upon, employing during this period different forms of anesthesia. In this way we used avertin and nembutal as preliminary sedation or basal anesthesia, local novocain infiltration and nerve blocking, nitrous oxide and oxygen (with or without ether), cyclopropane and intravenous evipal. In consequence, we believe, of the rather unusual nature of cases submitted to us for operative interference, our death rate was high and the number of bronchogenic spreads was, also, high.

Of the first 27 cases, 15 of which showed bilateral active disease, two died soon after operation, one on the seventeenth day from hemorrhage, and four within six weeks of the time of operation as the result of spread of the disease and the onset of acute pneumonic phthisis. There were altogether during this period eight cases in which more or less massive spread of the disease occurred.

The results of operative interference in the early group of cases operated upon in our institution was such that we were depressed and disappointed. It seemed that, especially for the type of case presenting itself at our clinic, inhalation anesthesia was too likely to be followed by unfavorable sequelae to justify the continuation of such anesthesia unless a substitute was not available. Despite the absence of favorable reports from other clinics regarding the use of high spinal anesthesia, we felt that were it possible to carry out such a procedure with relative safety during the operative period the patients might and should be better in so far as postoperative unfavorable sequelae were concerned. As Shields[2] had previously stated: "In the presence of

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pulmonary tuberculosis spinal anesthesia would be chosen by many should they be faced with an abdominal operation."

Commencing, therefore, in the summer of 1936, we have employed, routinely, spinal anesthesia for performance of extrapleural thoracoplasty and the induction of extrapleural pneumothorax. Spinal anesthesia has been employed for all first and second stages and, in many cases for the third and fourth stages—if the latter have been required.

In this way we have operated upon 42 cases. Twenty-four have shown active bilateral disease and eight were cases of tuberculous empyema. There have been two deaths in the operating room. In addition, we have had three disturbing experiences in the operating room. All three of these cases were similar, and the report of the case exhibiting the most severe reaction is presented in some detail. There have been three slight spreads or reactivations; in all three of these, however, the condition has promptly subsided. Apart from the two deaths in the operating room, we have had no deaths within two months from the date of operation.

Case Report.—Hosp. No. 3234; G. P., female, age 19, married, was admitted to the Grace Dart Home Hospital, September 14, 1937, with a history of onset of disease two years previously. At time of admission, patient had history of cough, marked loss of weight, blood-streaked sputum; slight infiltration right apex, and active disease involving upper third of left lung. Sputum was negative. She left hospital against advice and was readmitted September 13, 1938, at which time there was an incomplete pneumothorax on the left side. The upper two-thirds of the left lung showed active disease with an adherent apex which had failed to collapse under pneumothorax. The right side appeared stationary.

Operation.—September 28, 1938: A left-side extrapleural pneumothorax was attempted under spinal anesthesia. Approximately four inches of the fourth rib were resected and separation of the parietal pleura from the endothoracic fascia was accomplished. When the procedure was all but finished, patient stopped breathing and within a very few seconds the heart stopped beating.

A sterile towel was rapidly plugged into the wound and the patient turned on to her back. One cubic centimeter of adrenalin was then injected into the heart through the fourth interspace, just to the right of the sternum. The heart commenced to beat within a few seconds after the adrenalin injection. Artificial respiration was carried out, approximately four minutes later the respiratory rate returned to normal, within ten minutes the blood pressure was sufficiently high and the heart sufficiently strong for the operator to continue the surgical procedure. It is important to note that as soon as respiratory and cardiac failure occurred the patient was placed in the Trendelenberg position.

First hour postoperative: Respirations were shallow. There were spasms involving arms, head and neck. These spasms lasted a few seconds and occurred approximately every half hour. They were associated with crying and screaming spells. The following day, the spasms continued with decreasing frequency and, approximately 12 hours after the incident had occurred, the patient was able to understand spoken words but was unable to speak intelligently. She was cooperative but was unable to remember events immediately preceding the operation and had no memory of daily events. Within one week her memory for current events returned to normal, although there was no return of memory concerning events that occurred four days prior to operation. She was transferred October 20, 22 days after her operation, to a convalescent institution, at which time her mentality was normal and her wound well healed.

Of the 42 cases in the spinal group, there were 37 thoracoplasties and five inductions of extrapleural pneumothorax. In all, 99 operations have been carried out under spinal, and 12 under local anesthesia.

As previously reported, Etherington-Wilson's[3] technic, as described by him before the Royal Society of Medicine in London, in 1933, has been employed with the modifications as described by Bourne and O'Shaughnessy,[4] in 1936.

The technic employed at present is as follows: The patient is supported sitting upright by assistants. Nupercaine in 1:1500 solution is employed for anesthesia. The needle is introduced between the second and third lumbar spines and from 12 to 13 cc. are introduced somewhat slowly without barbotage. From the commencement of the time of injection a stop-watch is started and time allowed for the passage of the solution upward.

Although it would perhaps be more scientific were we able to state the exact number of seconds during which the solution is allowed to rise in the spinal canal, based upon the length of the patient's back, in centimeters, we have, hitherto, simply noted the patient's back to be either long, short or medium. The length of time allowed for the rise of the solution has been as a rule from 50 to 55 seconds with an absolute maximum of 60 to 65 seconds. It is of assistance to the anesthetist if the time is called off by an assistant at five second intervals. As soon as the length of time previously decided upon has been reached the patient is immediately laid down with the head and upper part of the torso inclined at an angle of about 20° downward from the flat.

As previously reported, it is believed that:

(1) Ten cubic centimeters of nupercaine solution (1:1500), 20 to 25 seconds, anesthetizes the first lumbar nerve segments—suitable for operations upon the lower limbs and the perineum.

(2) Twelve cubic centimeters of nupercaine solution (1:1500), 30 to 35 seconds, anesthetizes the tenth thoracic segments—suitable for operations upon the lower abdomen and pelvis.

(3) Fifteen cubic centimeters of nupercaine solution (1:1500), 40 to 45 seconds, anesthetizes a high zone, fifth thoracic segments—suitable for operations upon the upper abdomen and lower thorax.

As the result of our continued experiences since our first publication, we wish to modify the statement made with regard to the amount of material to be injected. We now believe that 15 to 17 cc. of nupercaine solution is too large and have come to the conclusion that 12 to 13 cc. is both adequate and accompanied by a greater measure of safety. It would seem from our experiences that 12 to 13 cc. of 1:1500 nupercaine solution, allowed to rise for 50 to 55 seconds in all but the longest backs, suffices to affect the lower cervical segments and so render anesthesia complete for the removal of the first rib and apicolysis in accordance with Semb's recommendation.

Although, hitherto, we have not attempted to estimate the specific gravity of the cerebral fluid, this, as is well known, varies somewhat. It is usual for

the specific gravity of the cerebral spinal fluid to be 1.007, although it is sometimes higher. Since the specific gravity of the nupercaine solution used is 1.003, and since we are dependent upon the difference in specific gravity of the two solutions for the height to which the anesthetic solution will rise in a given length of time, we propose in the future determining the specific gravity of the cerebral spinal fluid and intend to use for this purpose Barbour's[5] falling-drop method.

We have continued to use the preoperative medication substantially as recommended in our previous contribution. Ninety minutes before operation the patient receives morphine, Gr. ¼ and hyoscin, Gr. $\frac{1}{100}$, subcutaneously. Twenty minutes before operation the patient's condition is checked, and if, as is usually the case, he, or she, is not sound asleep the same dose is repeated. In consequence of this rather heavy sedation the patients are uninterested during the induction of the anesthesia and have a substantially complete amnesia regarding their experiences in the operating room. At the same time, almost immediately following operation, it is possible to wake them up and to obtain cooperation in the sense of ingestion of fluids and purposeful deep breathing and coughing. We believe that with increased doses of the two drugs mentioned nausea is less likely to occur and that there is less shock. We have not continued the use of atropine.

Since we are of the opinion that the two deaths which occurred in the operating room were due to the systemic effects, especially with reference to vasomotor reaction, and not to the effect of the anesthesia within the spinal canal, we have become more willing to employ analeptics early during the period of anesthesia. In any event, it must be stated that if analeptics, as for instance ephedrine, are to be withheld until such time as they are proven to be necessary, the care with which the patient is watched must be faultless. When analeptics are withheld until required, and it may be said that this is our usual procedure, ephedrine and the pressor principle of the posterior pituitary are administered intravenously and together. The dose of these two drugs is ephedrine 0.5 cc. (¾ Gr.), pitressin 0.5 cc.

At the completion of the operation strychnine Gr. $\frac{1}{30}$ is administered and repeated every three hours for three doses. This procedure has been carried out, in accordance with the teachings of Yandell Henderson,[6] for its effect upon skeletal muscle. Immediately upon return to the ward, patients have received 1,000 cc. of 5 per cent glucose in saline solution to which 10 units of old (unmodified)[7] insulin have been added. In but two cases has it seemed advisable to employ transfusions postoperatively; both of these cases had been suffering from massive pulmonary hemorrhage prior to operation.

Upon return to the ward, the patients have been allowed to sit up and their cooperation asked for. There has been early return of appetite, so that in this respect, at least, the depressing effect of operation has been in large measure overcome. Postoperative headache has been consistently absent.

In our earlier contribution we tabulated the advantages and disadvantages of spinal anesthesia for extrapleural thoracoplasty. With further experience

in the employment of the method, we copy with but few modifications the memoranda from our first paper.

(1) The patient does not lose consciousness, although under the conditions of premedication which we employ sleep is induced and a substantially complete amnesia follows.

(2) It is possible to induce the patient to cough, upon instruction. The respiratory effort, particularly if oxygen be administered, is as quiet as may be expected by any form of anesthesia.

(3) Owing, presumably chiefly, to the drop in blood pressure and the quiet, tranquil respiratory effort, there is less bleeding, we believe, during the course of the operation; at the same time we have not noted any tendency, whatever, toward postoperative hematoma accumulation.

(4) In consequence of the quietness of the chest wall and the complete muscle relaxation—of special importance in removal of the transverse processes—and the smaller amount of bleeding, operation can be performed more easily and more expeditiously, therefore, more safely.

(5) On return to the ward, cooperation on the part of the patient can be obtained at once, particularly in the sense of deep breathing and purposeful coughing.

(6) Although we have made a practice of administering strychnine, and 750 to 1,000 cc. of 5 per cent glucose in normal saline, to which 10 units of insulin have been added, as a routine in all cases immediately upon return to the ward, this has not been done on account of shock phenomena being exhibited.

(7) Patients have been able to commence the ingestion of nourishment within two or three hours after operation, in all cases, and have been able to return to full diet with the lapse of a very much shorter period of relative starvation than in cases in which other anesthetics have been used.

(8) The induction period, after the patient arrives in the operating room, is a short and simple procedure.

Objections.—(1) Although the patients do not suffer pain, a few have grunted when traction on the ribs has been made. Using scopolamine and morphine, patients have difficulty in remembering such an incident on the day following operation.

(2) There would appear to be a risk of involvement of the phrenic roots; such interference with functioning of the diaphragm has not been noted in any of our cases presumably because the anesthetic is so dilute when it reaches the midcervical region that motor function is not completely destroyed. Should such an accident develop, it would seem probable that serious results might well be avoided by the employment of artificial respiration or intratracheal insufflation.

(3) In our previous communication, we note that the possibility of severe circulatory disturbance must be considered, although at that time we had had no disturbing experience. As noted in this paper two patients have died and three others suffered important circulatory failure. Since we believe

that prompt administration of stimulants to the cardiac system is capable of correcting such failure, it becomes of special importance in such cases that more than usual caution on the part of the anesthetist in the observation of his patient is imperative.

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INTRAVENOUS AND REGIONAL ANESTHESIA*

JOHN S. LUNDY, M.D.

SECTION ON ANESTHESIA, THE MAYO CLINIC

ROCHESTER, MINN.

I APPRECIATE this opportunity to take a short part in this symposium on anesthesia, and believe that your choice of the subject of anesthesia for the symposium is significant of the development of anesthetic agents and methods during the last decade. I would like to mention briefly some of my own experiences in and reactions to this development.

The change from the scanty equipment necessary for the use of volatile anesthetics occurred as more and more complicated mechanisms were devised for the use of gaseous agents alone or in combination with volatile agents. At the moment, the modern gas machine is an expensive piece of equipment and is relatively complicated, but its economy and efficiency of operation have justified its high cost. It serves as a device for the administration of oxygen and combinations of oxygen and carbon dioxide and of oxygen and helium, as well as for the purpose of producing anesthesia. Artificial respiration is effectively carried out by intermittent compression of the breathing bag for the insufflation of oxygen. The skillful use of such a machine requires considerable instruction and practice on the part of the anesthetist, and further improvement may be looked for in these machines. This will be necessary, because of the inherent dangers associated with the use of inflammable and explosive anesthetics and the need for control of this hazard.

The introduction of such an agent as tribromethyl alcohol (avertin) has greatly increased the usefulness of the rectal method of anesthesia. Other agents have been tried, and this method has yet to have its greatest day of usefulness. Local and regional methods of anesthesia have had alternate periods of popularity and unpopularity. Factors that have influenced this have been the periodic introduction of promising agents and of modifications of technic that have increased the safety and satisfaction with which the methods were used. The intravenous method of anesthesia has slowly developed into a useful method.

The field of anesthesia has gradually broadened so that the limits of usefulness of the anesthetist rest largely on his willingness to apply himself. In the preoperative period he has been useful as a member of the surgical team in preparing the patient for anesthesia and for operation. During anesthesia, because the surgeon and his assistant are fully occupied with the technical steps of the operation, the anesthetist has been the most readily available person to carry out whatever measures are necessary to support the patient; for example, transfusion of blood or in the intravenous administration of

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solutions of acacia or other fluids. There has been a striking change in the method with which such treatment may be carried out. Previously some one of the surgical team would cut down on a vein and administer the solution. The confusion in connection with this procedure varied with the frequency with which it was carried out and the excellence of the team work exhibited. To-day, the anesthetist is ready to insert a 15 gauge needle, which contains a stylet, into a vein just as soon as anesthesia has been induced and just prior to the beginning of the operation. The point at which the veins are usually well filled with blood is most readily available for venipuncture. If during the course of operation, there is need for blood or fluids, there is no confusion or delay in withdrawing the stylet from the needle and permitting the solution to enter the vein. The large gauge of the needle permits the very rapid introduction of large quantities of solution, and at the same time the flow can be regulated by a pinchcock. Because of the anesthetist's experience with the use of the laryngoscope and the introduction of the intratracheal tube, he has learned to clean the respiratory passages, at the end of the operation, by means of an aspirating catheter. A few anesthetists have had training in the use of the bronchoscope and are of invaluable service in the postoperative period in the event that postoperative bronchoscopy is needed for relief of collapse of a lung. The supportive treatment of the patient in the postoperative period, in the event that such measures are necessary, may be carried out by the anesthetist.

The ready availability of the anesthetist in the hospital has been a factor in his usefulness as a supervisor in cases in which oxygen therapy and prolonged artificial respiration are required. This is particularly advantageous in obstetric practice when the newborn infant may need assistance to establish adequate pulmonary ventilation. The study of analeptic and supportive drugs has been impressed upon the anesthetist. For those patients who suffer intractable pain the anesthetist has collaborated with the attending physician in the control of such conditions. He has found a use for his methods of regional anesthesia as diagnostic procedures and as therapeutic procedures in certain cases.

The frequency with which he has been carrying out venipuncture has very naturally made skillful venipuncture available to hospitalized patients generally, and is particularly appreciated by those patients in whom this is ordinarily very difficult. Perhaps intravenous administration of fluids and drugs has been employed for a long time in a given case and most of the veins are thrombosed and are not usable. Even in these cases, venipuncture may be easily carried out by the proper application of heat and by the use of warm antiseptic solution, local anesthesia, a properly selected sharp needle, and utilization of tourniquet not only to dilate the vessel but also to anchor it so that it may be put on the stretch and easily entered with the needle. A knowledge of the situation of readily available veins in the body comes to the experienced individual and is of advantage to the patient; for example, the most readily available vein in the child who is one year of age is often

in the back of the hand and wrist, or it may be the saphenous vein near the internal malleolus.

These illustrations of the functions that the anesthetist can carry out call to mind the bright hope for the future development of this branch of medicine. A sign[1] of what may be expected in the future has been the recent approval of the American Board of Anesthesiology, Inc., an affiliate of the American Board of Surgery, by the Council on Medical Education of the American Medical Association. It is a genuine satisfaction to see the eagerness with which the requirements of this Board are being met, and the stimulus it is to many of those who have perhaps not kept up with modern trends as well as they might have. I anticipate that beneficial results will appear from the studies carried out by the various candidates who wish to prepare themselves for examination by the Board.

It seems to me unnecessary to stress the technical means of blocking the various nerves. Not much of skill in one's fingers can be transmitted by word of mouth. I am limiting my remarks purposely to some of the points that I have been asked to consider.

Intravenous Anesthesia.—The intravenous method of anesthesia is the newest and probably the most interesting method at our disposal. The method was begun in 1872, when Oré, of Lyons, used chloral hydrate. Since that time other drugs such as hedonal (methyl-propyl-carbinol-urethane), ipral (calcium ethylisopropylbarbiturate), alcohol in physiologic saline solution, ether in physiologic saline solution, sodium amytal, pentobarbital sodium (nembutal) and many other barbiturates have been used. Most of these drugs are no longer used in intravenous anesthesia. At this time, evipal (n-methylcyclohexamyl methyl barbituric acid) and pentothal sodium (sodium ethyl 1-methyl butyl thiobarbituric acid) are the drugs that are most frequently used for this purpose. The German product evipal (evipan) is available throughout the world; pentothal sodium has been available principally in the United States and the British Empire. The outstanding chemical difference between evipal and pentothal sodium is that the latter contains sulphur and evipal does not. This is of increasing importance, since it has been noted that persons who have been prepared for operation by the use of sulfanilamide should not be given pentothal sodium until a day has passed since the last sulfanilamide was taken. Damage to the liver by sulphur, with resultant jaundice and general malaise, has been noted in such instances. In such cases evipal in 2.5 per cent solution may be used; one must bear in mind this particular difference in the two agents.

For some time, it was advised that preliminary medication should not be employed prior to the use of intravenous anesthesia with either evipal or pentothal sodium. I think it is safe to say that the general consensus now is that preliminary medication should be used. It does reduce the amount of the anesthetic agent necessary to produce anesthesia, and the recovery period is shorter and the patient is more quiet. The journey to the operating room is less annoying to the patient. It is safer to use preliminary medication with

a barbiturate than it is to use a large amount of the barbiturate alone to produce anesthesia. There is, in general, a class of operations, such as removal of a single tooth, removal of packs, lumbar puncture and operations in which the pain must be abolished for only five minutes or less, in which no preliminary medication is necessary.

The use of intravenous anesthetics should entail the use of as dilute a solution as can be used effectively. Pentothal sodium at first was used in a 10 per cent concentration, but the site of injection became sore and painful if any of the solution was injected extravenously. A 5 per cent solution was substituted and apparently was just as satisfactory as the 10 per cent solution in the induction of anesthesia, but once in about 1,000 cases a phlebitis would develop one to three weeks after operation and would last for two weeks to three months. For this reason, I substituted a 2.5 per cent solution for the 5 per cent solution. I now prefer this mixture instead of the 5 per cent or 10 per cent solution as it induces anesthesia more slowly and more safely. The patient does not complain of the induction being so sudden as when a 5 or 10 per cent solution is used. The incidence of phlebitis has been reduced to about one in 3,000 cases. Two interesting cases illustrate the less irritating properties of the 2.5 per cent solution as compared with the 5 per cent concentration. In one case, a 5 per cent solution of pentothal sodium was injected intra-arterially and the patient complained of an intense smarting sensation in the hand during induction of anesthesia. At a later date a 2.5 per cent solution was injected intra-arterially and the patient complained of only a little discomfort in the hand before anesthesia appeared. Intra-arterial injection should be avoided.

I will now refer to another change in technic in the use of evipal and pentothal. It was common practice to inject a dose sufficient to anesthetize the patient and then immediately to inject a second dose equal to that which was sufficient to induce anesthesia. The needle then was removed and the operation carried out under whatever anesthesia occurred as a result of the dose administered. The next improvement in technic was to use the intermittent method of injecting the solution; that is, to maintain the point of the needle within the lumen of the vein, and, after anesthesia had been induced, to inject small amounts as necessary to maintain anesthesia. This technic was similar to the administration of ether by the open drop method; the agent was applied when and in such doses as were needed. This technic allowed the drug to be used for very much longer operations than did the earlier technic, which consisted of one or two injections.

However, since the patient was inhaling only air, it was found necessary to keep the respiratory passages patent continuously, as the effort to breathe was not vigorous. A paper or the use of a cotton "butterfly" over the nose was considered a help in recognizing that definite exchange of air was taking place, and this is still useful. It was decided that this type of anesthesia should not be used for children because of the smallness of the respiratory passages and because pulmonary ventilation often was inadequate when only air was

breathed. In certain cases in which respiratory depression became prolonged and anoxemia was evident, it was found advisable to carry on artificial respiration by using oxygen from the anesthetist's gas machine. It soon was noted that if the oxygen was administered throughout the period of intravenous administration of the anesthetic agent, respiration was more vigorous and the effectiveness of the pulmonary ventilation could be noted by watching the respiratory exchange as the bag emptied and filled. The administration of oxygen also tended to improve the color of the patient. This was particularly true in cases in which there was cardiac disease and no period of anoxemia could be permitted. These patients did very well during the period of anesthesia and it can now be said that the safest technic is to administer oxygen to these patients as soon as anesthesia has been induced and until they begin to show signs of recovery. When this technic is used, the amount of the barbiturate which may be administered can be greatly increased and more profound anesthesia and relaxation can be secured. As a result of applying this technic of intravenous anesthesia, the method has been extended in some places in major abdominal operations and to its use in cases in which the patients are small children. The technic now used may be said to be at this point of development, but within the year one may expect to see further advances. In time, as new drugs are introduced and more experience is gained with the method, many of the problems of anesthesia no doubt may be solved. A good illustration of one problem in anesthesia is the elimination of the hazard associated with the use of inflammable and explosive inhalation anesthetic agents.

One of the most promising modifications that we have employed recently at the clinic is the use of pentothal sodium in inducing anesthesia prior to using inhalation anesthetics, especially in cases in which the patients are hypertensive individuals who have almost always resisted the induction of anesthesia, who often have had exaggerated stages of excitement during induction and who also have had periods of extreme cyanosis which are undesirable in the presence of high blood pressure. These patients usually respond very nicely to an intravenous injection of pentothal sodium; 3 or 4 cc. and never more than 10 cc. of a 2.5 per cent solution should be administered. It is better to give an underdose than it is to administer an overdose, as otherwise the respirations may become too shallow during the induction of anesthesia by inhalation. After the patient shows signs of drowsiness and perhaps even stops counting, the gas mask is applied to the patient's face and nitrous oxide and oxygen is administered simultaneously with an injection of 1 cc. of a 2.5 per cent solution of pentothal sodium about every 15 seconds. The respirations are watched all the time to see that breathing does not stop or is not markedly depressed. The results of this method are rather spectacular. The patient shows little or no signs of excitement, the blood pressure is decreased during the period of induction, as compared to the usual marked increase. The intratracheal tube may be introduced in about five or ten minutes, whereas previously it has taken two or three times as long. The amount of anes-

thetic (drop ether) used is about two-thirds as much as is necessary when no pentothal sodium is used. Patients have usually not become nauseated and have not vomited afterward. Shock is usually not in evidence postoperatively, although where extensive sympathectomy has been performed, the blood pressure may be more definitely lowered than it is in other cases.

The use of analeptic drugs for relief of respiratory depression has been tried with apparent success. The present status of the effects of several commonly used stimulants is controversial. However, I feel that such drugs as coramine (a 25 per cent solution of pyridine betacarbonic acid diethylamide), metrazol (pentamethylene tetrazol), ephedrine and epinephrine may serve to support a depressed patient if used in addition to other measures. The route for the administration of the stimulant is the intravenous one.

Regional Anesthesia.—The effects of regional methods of anesthesia have been increased by the substitution of metycaine [benzoyl-γ-(2-methylpiperidino)-propanol hydrochloride] for procaine. There are certain reasons why this occurred; one is that metycaine is a surface anesthetic as well as one effective by injection. The other reason is that the substitution of a 1 per cent solution of metycaine for a 1 per cent solution of procaine is not actually a substitution of an equivalent concentration. A 1 per cent solution of metycaine is approximately equivalent to a 1.25 per cent solution of procaine, so that in the statement that metycaine is more effective than procaine it must be admitted that the concentration of metycaine is relatively stronger than the concentration of procaine. The fact that metycaine is a surface anesthetic as well as an injectable one makes it of great value to the anesthetist, for the one outstanding unsatisfactory characteristic of procaine is that it is not a good surface anesthetic. It has been hoped that an agent could be produced with which one could carry out any method of local anesthesia. Metycaine is the nearest approach to this of any agent that has been developed up to this time. It was felt that metycaine would be a particularly satisfactory drug as a spinal anesthetic, and I admit that it is a good agent and that the anesthesia can be made to last longer than with procaine, but for operations which are to last an hour or less I still prefer procaine as a spinal anesthetic agent.

In various blocks, however, such as sacral block, cervical block, brachial plexus block, block anesthesia of the digits and field block, especially of the scalp, metycaine in a 1 per cent solution is definitely more satisfactory than a 1 per cent solution of procaine. I also should like to point out that in sacral block one finds results to be very much more encouraging with metycaine than with procaine. I prefer sacral block over spinal anesthesia for operations on the anus, because of the elimination of lumbar puncture headache. My experience with headache of this type has been that while it does not occur apparently as frequently as it did some years ago, one occasionally sees a patient who complains bitterly of headache for as long as two years after the operation. I have never been convinced that headache which lasts as long as this is very debilitating because subsequent events show that the period of recovery usually begins when unhappy circumstances in the life of the patient

are altered. Patients also complain very bitterly of headache with the hope that they can avoid paying the doctor's fee. In transurethral operations I have advocated the use of sacral block instead of spinal anesthesia because when undue distention of the bladder takes place the patient complains and in the event of spinal anesthesia the patient usually is not aware of the overdistention of the bladder. On the other hand, the surgeon has been better satisfied with spinal anesthesia and has become accustomed to avoiding marked overdistention of the bladder; under those circumstances spinal anesthesia is satisfactory. Here again, however, the question of headache has to be considered. The most persistent instance of headache that I have encountered was subsequent to one of these operations and spinal anesthesia.

For operations on the digits and when field block is used, it will be found that the metycaine will give postoperative relief of pain for several hours in most cases, while procaine does not. Most persons who have an idiosyncrasy to procaine and have a so-called novocain dermatitis can use metycaine without untoward results.

For celiotomy, especially on the upper part of the abdomen, I know of no block that is better than abdominal block, combined with gas, or gas and ether as an inhalation anesthetic, and moderate preliminary medication. The block of the abdominal wall may be carried out with a 0.5 per cent solution of procaine or metycaine, which should contain a small quantity of epinephrine (6 minims of 1:1,000 solution in 200 cc. of the anesthetic solution). The block should be done 15 to 20 minutes before the incision is to be made so that there is an opportunity for the solution to soak into the tissues and permeate entirely the terminations of the intercostal nerves. Under such circumstances it is presumed that the injection of the solution into the abdominal wall will be made when the general anesthesia has been induced. The general anesthesia may be lightened or discontinued as soon as the peritoneum has been closed.

To combine local and general anesthesia is often desirable, but when spinal anesthesia is combined with general anesthesia it is best in my experience to give the spinal anesthetic at least 10 to 15 minutes before administration of the general anesthetic is started. If in the course of the operation spinal anesthesia becomes sufficiently high so that the patient becomes dyspneic, one will find that respiration becomes very annoying as the patient makes the vigorous effort necessary to ventilate himself. There is danger that the induction of general anesthesia, taking place simultaneously with the production of spinal anesthesia, will bring the patient into a dangerous degree of narcosis when the spinal anesthesia has produced its maximal effect and the general anesthesia has produced its maximal effect. I have seen one fatality because of such an occurrence.

For the support of the blood pressure during spinal anesthesia, I prefer to inject intramuscularly 25 mg. of ephedrine just before spinal anesthesia is induced, and to administer 25 mg. of ephedrine intravenously during anesthesia if the systolic blood pressure falls below about 85 Mm. of mercury.

Individual variations in the patient's reaction to the anesthetic and the stimulant may be more nearly balanced than by routinely using a larger initial dose of the stimulant.

The present need for a better noninflammable anesthetic has made the combined use of regional and intravenous anesthesia advantageous. Fortunately, most of the barbiturates have an antispasmodic action while most local anesthetics produce a spastic effect when the patient exhibits a toxic reaction. This antagonistic effect of a local anesthetic compared with an intravenous barbiturate makes their combined use one that tends to increase the safety of the use of each agent. In some instances the use of an intravenous anesthetic at first, followed by the blocking of the nerve trunks while the patient is unconscious, is greatly appreciated by patients.

Preliminary medication is advisable before regional methods of anesthesia are to be used. For the average adult, I like to give pentobarbital or nembutal, 1½ gr. (0.1 Gm.), the night before operation and repeat this dose about 7A.M. on the day of operation, and to administer ⅙ gr. (0.01 Gm.), of morphine and 1/150 gr. (0.0004 Gm.) of atropine by hypodermic injection, 40 minutes before the operation. This procedure is usually satisfactory. However, during the operation, if the patient seems to be suffering regardless of whether or not the anesthesia is beginning to wear off, of whether or not the operation is more extensive than planned for, or of whether or not the anesthesia is insufficient for the contemplated operation, a small dose of morphine will usually relieve the patient of his pain. In some cases the ordinary dose of morphine is insufficient and an additional amount of morphine is necessary to give relief. This should be given intravenously. The intravenous injection should be carried out very slowly and should be discontinued as soon as the patient feels some effect of the drug. If more is to be administered, a period of ten minutes should elapse before any further morphine is given intravenously. The usual dose for intravenous administration is less than the dose that is given subcutaneously. That is, if one would give ¼ gr. (0.016 Gm.) subcutaneously, one would administer ⅙ gr. (0.01 Gm.) intravenously. One-eighth grain (0.008 Gm.) of morphine intravenously is equivalent to ⅙ gr. (0.01 Gm.) given subcutaneously.

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SYMPATHETIC NERVE BLOCK AS AN ADJUNCT ANESTHESIA IN MINIMAL RESECTION OF THE STOMACH FOR PEPTIC ULCER *

WILLIAM FRANCIS RIENHOFF, JR., M.D.

BALTIMORE, MD.

FROM THE DEPARTMENT OF SURGERY OF THE JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

THE OBJECT of this report is twofold: In the first place, to present a series of consecutive cases of benign ulcers of the pyloric antrum and the duodenum which have been treated by partial gastrectomy, performed under a very light nitrous oxide and oxygen inhalation analgesia, combined with an intra-abdominal injection of a weak solution of pontocaine into the celiac plexus; and in the second place, to describe an operative technic, based upon anatomic and physiologic considerations, that combines safety and efficacy, as far as the immediate and late postoperative results are concerned, in a higher degree than the more conservative and also the more radical procedures.

Material.—The basis of this report consists of a series of 82 consecutive cases of pyloric and duodenal ulcer that have been operated upon by various operators employing the same surgical technic, but different methods of anesthesia. The operation in each instance has been a resection of only the pyloric antrum followed by a short loop antecolic gastrojejunostomy. Forty-four patients have been operated upon by different operators, under general anesthesia, *i.e.*, nitrous oxide and oxygen induction, followed by ether with a preceding basal anesthesia such as avertin. Five deaths occurred in this series, a mortality rate of 11.3 per cent, only one of which could be attributed to the operative procedure. In the latter case, the patient was found at autopsy to have developed an acute pancreatitis that might have been caused by the operative dissection of a large penetrating and indurated ulcer away from the head of the pancreas. Three deaths followed the development of bronchopneumonia and one, four hours after operation, during a generalized convulsion. The latter patient had been given a combined general anesthesia, *i.e.*, avertin and cyclopropane. Postmortem examination in all of these patients revealed *per primam* healing of the gastrojejunal anastomosis as well as the duodenal stump, so that in at least four, if not all five, the lowering of the patient's resistance and vitality due to the general anesthesia played a major rôle in causing their death.

In striking contrast to this is a series of 38 consecutive patients that were operated upon in whom, although the same surgical technic was employed as in the above series, sympathetic nerve block and analgesia was used in preference to general anesthesia (Table I). In this series no deaths occurred.

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

TABLE I

IDENTIFYING DATA RELEVANT TO THE 38 PATIENTS WHO RECEIVED SYMPATHETIC NERVE BLOCK

R. R., Hosp. No. 148480	F. R., Hosp. No. 148057
J. M., Hosp. No. 150340	E. S., Hosp. No. 106285
J. M., Hosp. No. 152636	B. G., Hosp. No. 143206
G. U., Hosp. No. 150914	B. D., Hosp. No. 143090
F. B., Hosp. No. 152775	H. M., Hosp. No. 111689
A. B., Hosp. No. 152908	C. S., Hosp. No. 110025
M. C., Hosp. No. 155005	N. H., Hosp. No. 72117
J. P., Hosp. No. 160111	J. J., Hosp. No. 72599
M. P., Hosp. No. 160146	L. Z., Hosp. No. 74631
R. W., Hosp. No. 160504	J. R., Hosp. No. 127170
J. S., Hosp. No. 163287	C. M., Hosp. No. 127529
H. B., Hosp. No. 100764	D. W., Hosp. No. 130947
C. W., Hosp. No. 143641	L. S., Hosp. No. 130930
W. Q., Hosp. No. 103075	B. C., Hosp. No. 170793
F. F., Hosp. No. 103106	J. G. Hosp. No. 170430
C. A., Hosp. No. 103163	R. S., Hosp. No. 170387
J. W., Hosp. No. 106035	C. H., Hosp. No. 167878
W. G., Hosp. No. 71840	C. M., Hosp. No. 168231
W. M., Hosp. No. 127682	L. M., Hosp. No. 164296

In four of this latter group, the patients had developed marginal ulcers following a posterior gastro-enterostomy previously performed elsewhere for duodenal ulcer. In two of these four, the marginal ulcers had penetrated the colon resulting in gastrojejunocolic fistulae. In the latter two cases, a resection of part of the jejunum and transverse colon was found to be necessary as well as a resection of the pyloric antrum and first portion of the duodenum. An end-to-end anastomosis was performed in both cases on the jejunum and colon. In the former two cases of marginal ulcer, the jejunum was simply closed and the stomach resection carried out as herein described. Even in these complicated cases there were no untoward respiratory or abdominal sequelae following the use of celiac sympathetic nerve block anesthesia.

Further advantages of combined local anesthesia and gas analgesia over general anesthesia will be alluded to under Discussion.

Anesthesia.—The present literature on the employment of a local, in combination with a very light gas anesthesia for abdominal operations is extensive. Crile,[1] in 1915, was the first to point out the advantages of anoci-association and the prevention of shock as well as many other postoperative complications by the use of a combination of local and very light gas anesthesia. Finsterer[2] has employed local and splanchnic nerve block anesthesia for years. For a complete bibliography of the development of the methods of local anesthesia in abdominal surgery, one should consult the monograph entitled Anesthesia in Abdominal Surgery, by Hans Finsterer, published in 1923.

The only modification of the previous methods to be noted in this report is the employment of a "light" gas analgesia while going through the abdominal wall and opening the peritoneal cavity. The patient is then allowed to rebreathe into the gas bag throughout the operation without further addition of

nitrous oxide. The celiac plexus is injected intra-abdominally at the level of the twelfth thoracic vertebra (Fig. 1) with 100 cc. of a 1:3,000 solution of pontocaine which is allowed to diffuse in the retroperitoneal tissue. In this manner a concentrically radiating area of retroperitoneal edema may be observed which extends over the visible area of the posterior peritoneal wall and

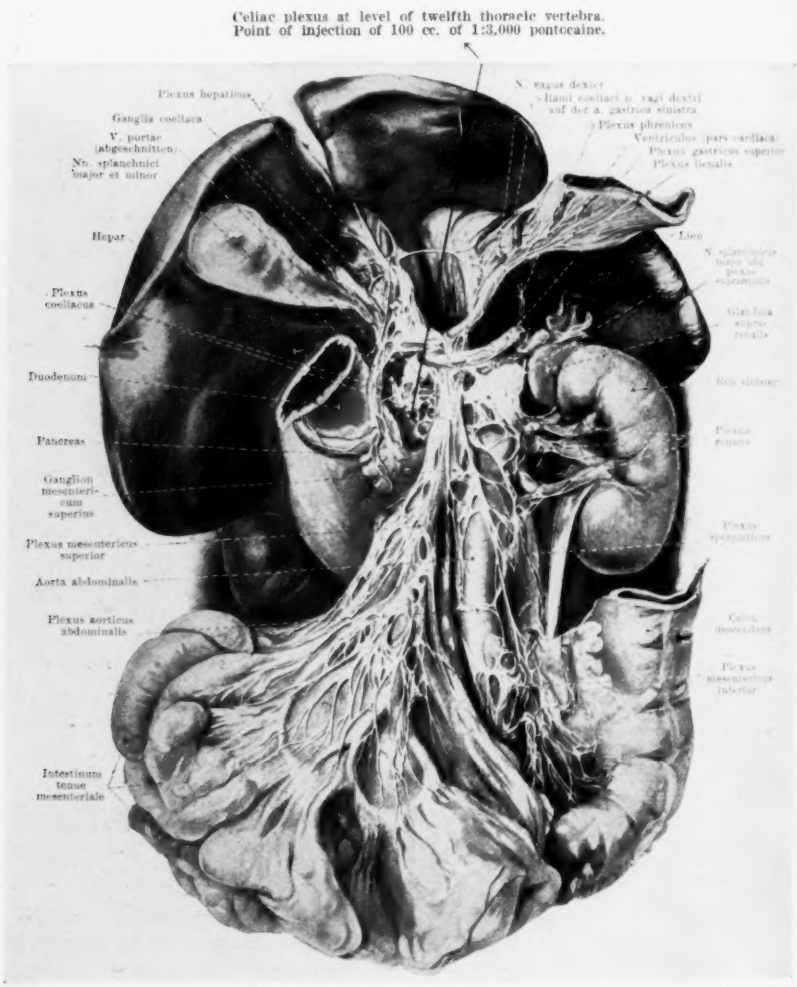

FIG. 1.—Abdominal plexuses of the sympathicus (Stalteholz, Hand Atlas of Human Anatomy, vol. 3).

bathes the entire celiac sympathetic plexus with the pontocaine solution. The technic of injection is greatly facilitated by the use of a long, guarded needle devised by Finsterer. The left hand is inserted into the supraduodenal fossa to the left of the gastrohepatic omentum. Just below the inferior surface of the liver, or portal hilus, the right border of the aorta is located with the index finger. The middle finger alongside the index finger will thus impinge upon the surface of the tissue lying between the aorta and the inferior vena cava.

The guarded needle is then inserted into the retroperitoneal tissues, being held in the right hand and guided by the groove between the middle and index finger of the left hand. The sharp point of the needle may be felt to engage the bony structure of the body of the twelfth thoracic vertebra. A 20 cc. syringe is attached and the needle very slightly withdrawn. A few cubic centimeters of the pontocaine solution are then injected, but the plunger is again withdrawn to be certain the needle point is not inside a blood vessel. If no blood is recovered in the syringe, the 100 cc. of the pontocaine solution are injected slowly over a period of about three minutes. Within a very short time the increased relaxation of the abdominal wall can be appreciated. Although the patient is receiving just enough nitrous oxide and oxygen to quiet him psychically, the degree of relaxation of the abdominal wall throughout the operation remains constant. There is no straining or tendency to become alternately light or deep as is so often the case with gas anesthesia when used alone without some supplement.

Operative Procedure.—The rationale for the operation employed in this series of cases is based upon anatomic and physiologic data, which seem to indicate that the lower fifth of the stomach or the pyloric antrum may truly be considered the "pacemaker" of this organ.

In 1906, Edkins[3] showed that a decoction made by boiling pyloric mucous membrane with acid or with water or with peptone and injected in small quantities into the jugular vein caused a secretion of gastric juice, containing both hydrochloric acid and pepsin. In order to produce this positive effect, it was necessary to employ pyloric mucous membrane from the lower fifth of the stomach. Extracts made from the mucous membrane of the remaining portions of the stomach proved to be ineffective. The secondary secretion of gastric juice is determined, not as Pavlov and Popielski[4] imagined, by a local stimulation of the reflex nervous apparatus in the gastric wall, but by a chemical mechanism. The first products of digestion act on the pyloric mucous membrane and produce in this membrane a substance which is absorbed into the blood stream, and carried to all the glands of the stomach, where it acts as a specific excitant of their secretory activity. This substance has been named gastrin and is a gastric hormone. This form of chemical stimulation for the formation of gastric juice persists long after the mental effects or memory of a meal has worn off, as well as the psychic secretion through the vagi, described by Pavlov.

As a result of numerous physiologic experiments since, the original observations of Edkins[3] have been corroborated.

The presence of gastrin in human postmortem pyloric mucous membrane has been demonstrated by Ivy, *et al.*,[5] and shown to be present to the same extent as in hogs' mucosa. The similarity of gastrin to histamine has been demonstrated by Koch, Luckhardt, *et al.*,[6] who think it is a basic imidazole derivative. Thus far pilocarpine and histamine are the only known imidazole derivatives which stimulate the gastric mechanism to secretion. Further, McHenry and Best[7] (1930), having developed histaminase, a histamine in-

activating enzyme, enabled Sacks, Ivy, *et al.*[8] (1932), to demonstrate that this enzyme will inactivate the active secretory agent in extracts of the pyloric mucous membrane. This again demonstrates the close relationship of this active principle, gastrin, to the imidazole ring. If one concedes that histamine and gastrin are identical, then the former produced in physiologic amounts by the pyloric mucous membrane may be viewed as not only being a specific hormone, augmenting and facilitating the formation of gastric juice, but also, as shown by Koskowski and Ivy[9] (1925), increasing the motor activity of the gastro-intestinal tract as well. This view is supported by Best and McHenry[7] (1930), on the distribution of histamine and histaminase in the tissues of the body. They found that the stomach and liver are the only organs examined in the body which contain relatively large quantities of histamine and which do not also contain histaminase. The enzyme is absent from the stomach and practically absent from the liver. From their work we can say that it is easily possible for the pyloric mucosa to liberate enough histamine into the portal blood and then into the general circulation to stimulate the production of acid by the gastric glands and to exercise synergistic action on the digestive process.

Removal of the pyloric antrum must, therefore, take away one, if not the major, factor in the stimulation of the formation of gastric juice, *i.e.*, acid and pepsin, as well as have a retarding influence upon gastric motility.

Although peristaltic waves begin in the cardiac end of the stomach, the incisurae produced by their contractions are very much deeper when they reach the lower fifth of the stomach. The pyloric antrum, on erect fluoroscopic examination in the majority of individuals, appears to be merely a continuation upward of the intestinal tube, when compared to the sac-like, relatively atonic, fundic portion of the stomach. Whether peristaltic waves of contraction may arise independently near the beginning of the pyloric antrum in the distal four-fifths of the stomach has not yet been proved, but it is an objective certainty observed fluoroscopically that the lower fifth of the stomach is far more active from the standpoint of the number of contraction waves, as well as the extent of their contractions. The difference in the thickness of the muscle layers of this region of the stomach, together with its well known triturating effect on food, would lead to the expectation of the observed increased contractility of this region. It would seem likely, in our present state of knowledge, that pain associated with ulcerative lesions of the stomach has its origin, in part at least, in the muscular spasm of the pyloric sphincter and antrum associated with the usual hyperperistalsis, hypertonicity and hyperacidity. Thus the relief of pain may in a large measure be directly attacked by the removal of this region of the stomach which manifests the rôle of an accelerator or amplifer of previously initiated muscular activity. In this manner three important steps have been taken in ridding the patient of an ulcer, and also in protecting him from the liability of a recurrence. These steps are: (1) The removal of the portion of the stomach which is most active, from the standpoint of motility and contractility, and therefore that portion the mucous membrane of which is subjected to the

highest incidence of trauma; (2) the ablation of the area of mucous membrane which is productive of a hormone similar to histamine, and responsible for, in contrast to the psychic secretion, the chemical secretion of gastric juice; (3) the shunting of gastric contents away from the remaining potential ulcer bearing area in the duodenum.

Operative Technic.—A midline incision has been employed (Plate I) because exposure of the lesser curvature of the stomach, and thus the left gastric artery and coronary vein, is more easily accomplished with less vigorous

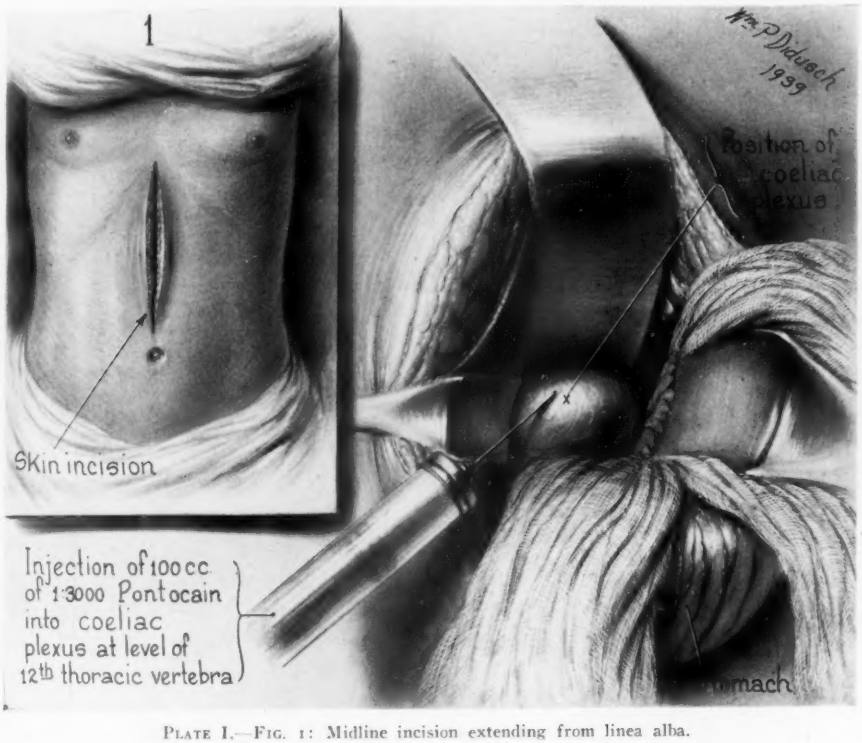
1
Wm P Diduch
1939
Position of coeliac plexus
Skin incision
Injection of 100 cc of 1:3000 Pontocain into coeliac plexus at level of 12th thoracic vertebra
mach

PLATE I.—FIG. 1: Midline incision extending from linea alba.

FIG. 2 shows posterior peritoneal wall with needle projecting into retroperitoneal tissue, at the level of the celiac plexus.

retraction by this route than through a high right rectus incision. The less the degree of retraction the better the relaxation of the abdominal wall. In the upper abdomen the midline incision traverses the linea alba which is the most avascular portion of the abdominal wall. Obviously, there is no interference with the nerve supply to the rectus muscle or further weakening of that structure from direct trauma in splitting its fibers. The round or falciform ligament of the liver lies immediately beneath the linea alba, but under the right lip of the incision, the reflection of the peritoneum to cover the ligament may be incised and the entire body, *i.e.*, ligament, fat and peritoneum, reflected laterally. When the peritoneum is incised somewhat to the right of the reflection of the round ligament, it is not necessary to suture the edges of

the former when closure of the abdomen is made. The round ligament falls into its normal position, covering the posterior surface of the wound as a peritoneal flap, when the linea alba and thus the abdominal wall is closed.

PLATE II.—FIG. 1: Stomach delivered through incision, showing position of ulcer in the posterior part of the second portion of the duodenum.

FIG. 2: Mobilization of the second portion of the duodenum, by incising the lateral peritoneum.

Following a thorough examination of the abdominal contents, the injection of the retroperitoneal tissues in the region of the celiac plexus is accomplished as described above (Plate I, Fig. 2).

The location of the common duct and its point of disappearance behind the upper part of the second portion of the duodenum has been made a

routine preliminary step in the operation. The knowledge of the position of this duct affords not only more confidence but also more safety in a liberal mobilization of the second part of the duodenum for resection of ulcers in this region. At the same time, such a free dissection enables the operator to effect a more secure closure of the duodenal stump (Plates II and III). The left gastric vessels and right vagus nerve are then divided and ligated with medium "c" silk. Following this, vessels running in the gastrohepatic and gastrocolic as well as the duodenohepatic and duodenocolic ligaments are individually clamped and ligated with "c" silk. Thus the entire lower fifth or pyloric antrum of the stomach, together with the first and upper two-

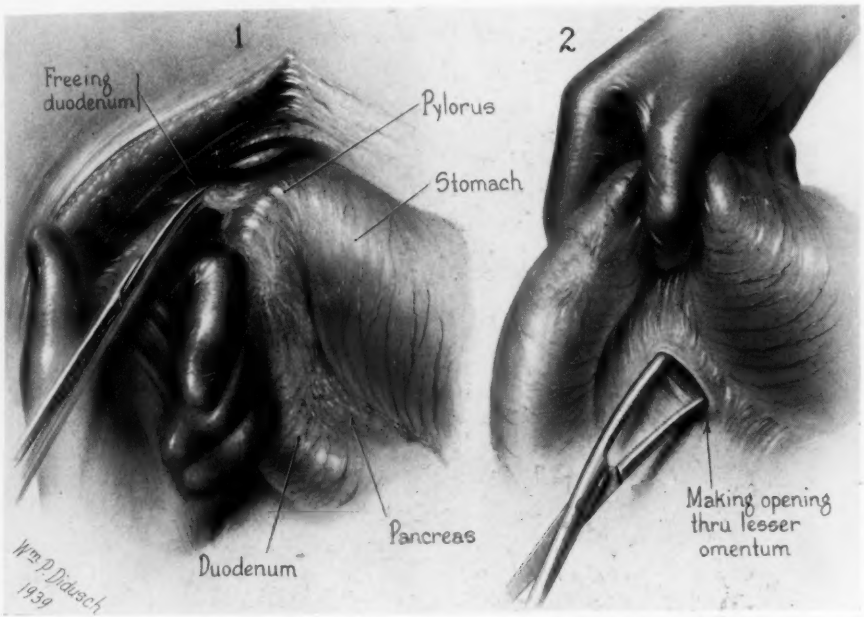

PLATE III.—FIG. 1: Further mobilization of the first part of the duodenum by separating the gastrohepatic omentum.

FIG. 2: Curved clamp inserted into opening of gastrocolic omentum, making an opening in the lesser peritoneal curvature.

thirds of the second portion of the duodenum, are thoroughly mobilized and the latter freed from the head of the pancreas. A medium sized Payr crushing clamp is now placed across the body of the stomach at approximately the junction of the fundus and the pyloric antrum (Plate IV). The stomach is divided and the posteromedial surface of the duodenum is freed from the head of the pancreas. Due to the fact that the common duct lies between the head of the pancreas and the medial wall of the duodenum, a large portion of the latter may be removed without danger of injury to the former. The duodenum, having been mobilized below the ulcerated area, is clamped across with a small Payr crushing clamp (Plate V). The pyloric antrum, pyloric sphincter, first and part of the second portion of the duodenum are then removed together with the ulcer. The stump of the duodenum is closed

with two layers of suture (Plate VI), the first a continuous suture of "0" chromic catgut. *This is placed underneath the crushing clamp in such a manner that the crushed tissue beyond it can be cut off without danger of*

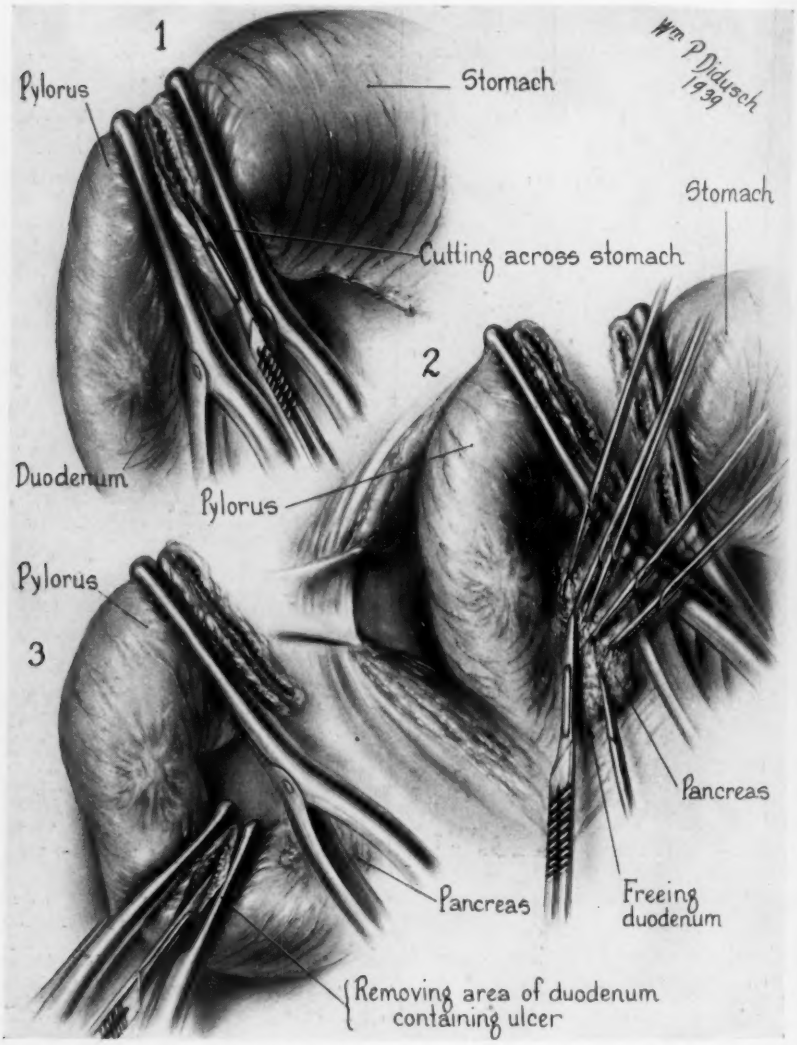

PLATE IV.—FIG. 1: Division of stomach just proximal to pylorus. This illustration is somewhat misleading, as more stomach is removed than demonstrated in this illustration. The impression from this would lead one to believe that less than the lower fifth of the stomach is excised. The proximal Payr clamp is also larger than the distal one on the duodenal side.

FIG. 2: Dissection of the pyloric end of the stomach and first portion of the duodenum from the head of the pancreas.

FIG. 3: Division across the duodenum in the second portion, removing that portion containing the ulcer.

cutting the suture line. The advantage of removing this crushed tissue, which will become necrotic, is obvious. With this type of suture only viable tissue is turned in. Interrupted Halsted sutures of fine "a" silk are then used to

invert the first continuous suture line. All bleeding points about the head of the pancreas are transfixed with fine silk. This procedure is felt to be important because the pancreatic tissue cut across in the freeing of the second portion of the duodenum may, if not sewn up, give rise to a drainage of

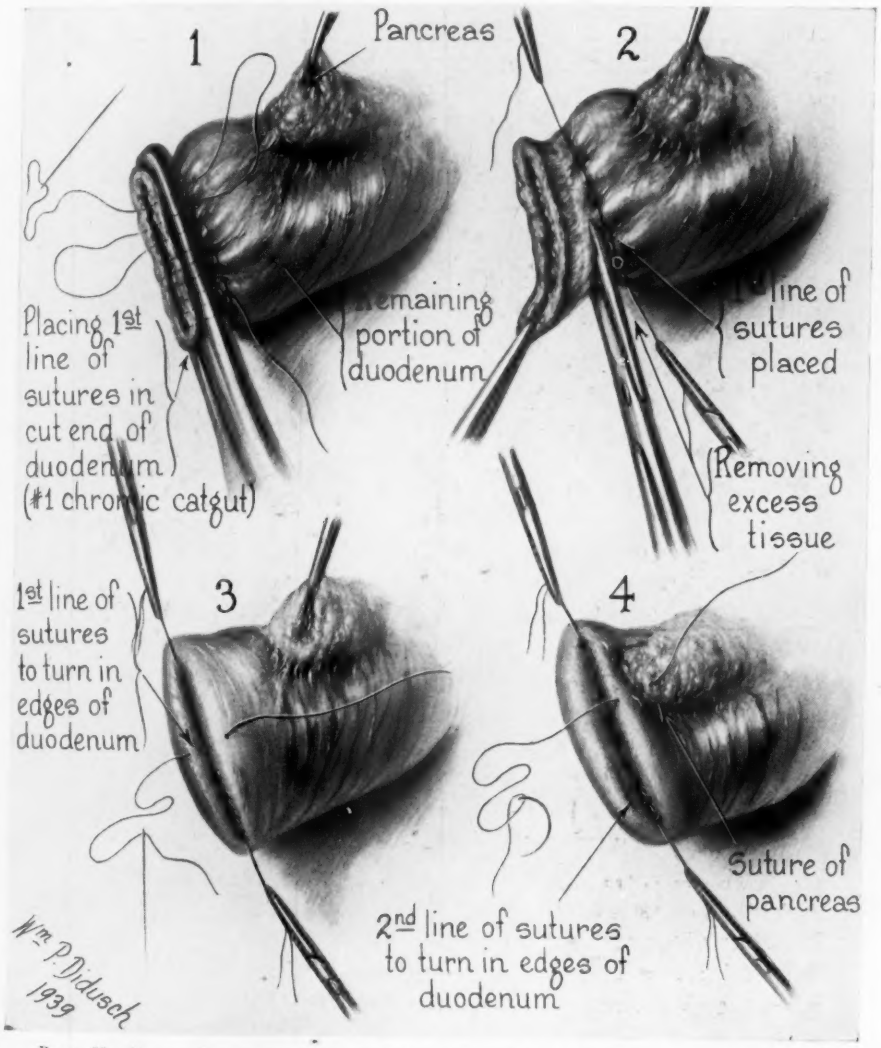
1
Pancreas
2
Placing 1st line of sutures in cut end of duodenum (#1 chromic catgut)
Remaining portion of duodenum
1st line of sutures placed
Removing excess tissue
1st line of sutures to turn in edges of duodenum
3
4
Suture of pancreas
2nd line of sutures to turn in edges of duodenum
Wm. P. Didusch 1939

PLATE V.—FIG. 1: Demonstrates the method of closure of the duodenum. A continuous mattress suture distal to the Payr clamp is placed so the crushed tissue can be excised, as shown in Figure 2, leaving only viable tissue to be turned in with interrupted silk sutures, as shown in Figures 3 and 4.

pancreatic ferments that will precipitate a peritonitis similar to that seen in acute pancreatitis. Care is taken to insert a small part of the beginning or extreme right portion of the gastrocolic omentum between the raw surface of the head of the pancreas and the duodenum, in order to prevent any possibility of digestion or erosion of the stump of the latter. Attention is

then turned to the reestablishment of the continuity of the gastro-intestinal tract. Due to the relatively small segment of stomach removed, a short-

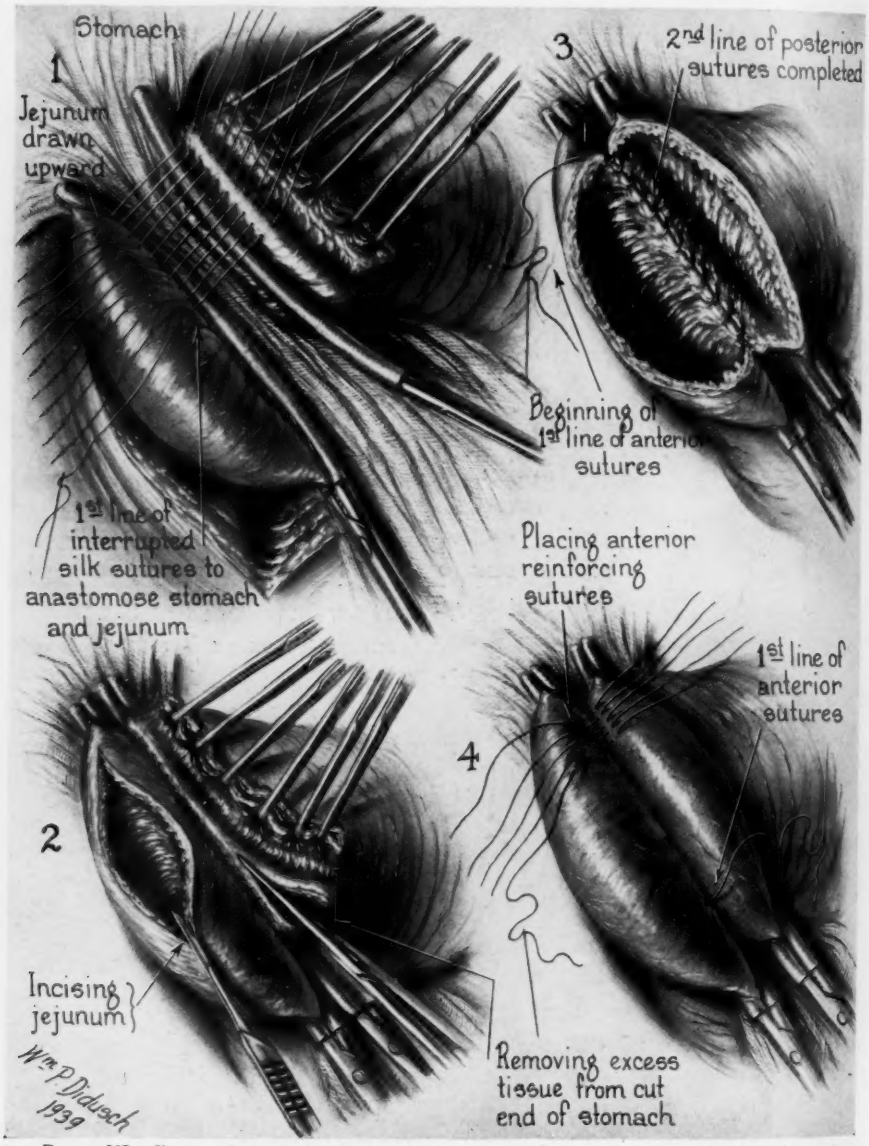

PLATE VI.—FIG. 1 demonstrates Halsted's interrupted sutures placed in position before tying, making up the posterior row. Also, the noncrushing intestinal clamps in place, both on the stomach and jejunum. A gauze net webbing is used as a sleeve over the clamp blades rather than rubber.

FIG. 2 demonstrates opening the jejunum, also trimming away of the crushed, devitalized tissue, resulting from the use of the Payr clamp.

FIGS. 3 and 4 show the inner and outer layer of sutures. The inner layer is continuous No. 1 chromic catgut.

looped antecolic gastrojejunostomy can be performed readily and without the necessity of an entero-enterostomy. The colon and greater omentum are

returned to the peritoneal cavity by shunting them to the left of the proximal loop of the jejunum. When this latter portion of the intestine is sewn to the cut end of the stomach, the distance between Treitz's ligament and the beginning of the gastrojejunal anastomosis at the lesser curvature of the stomach is

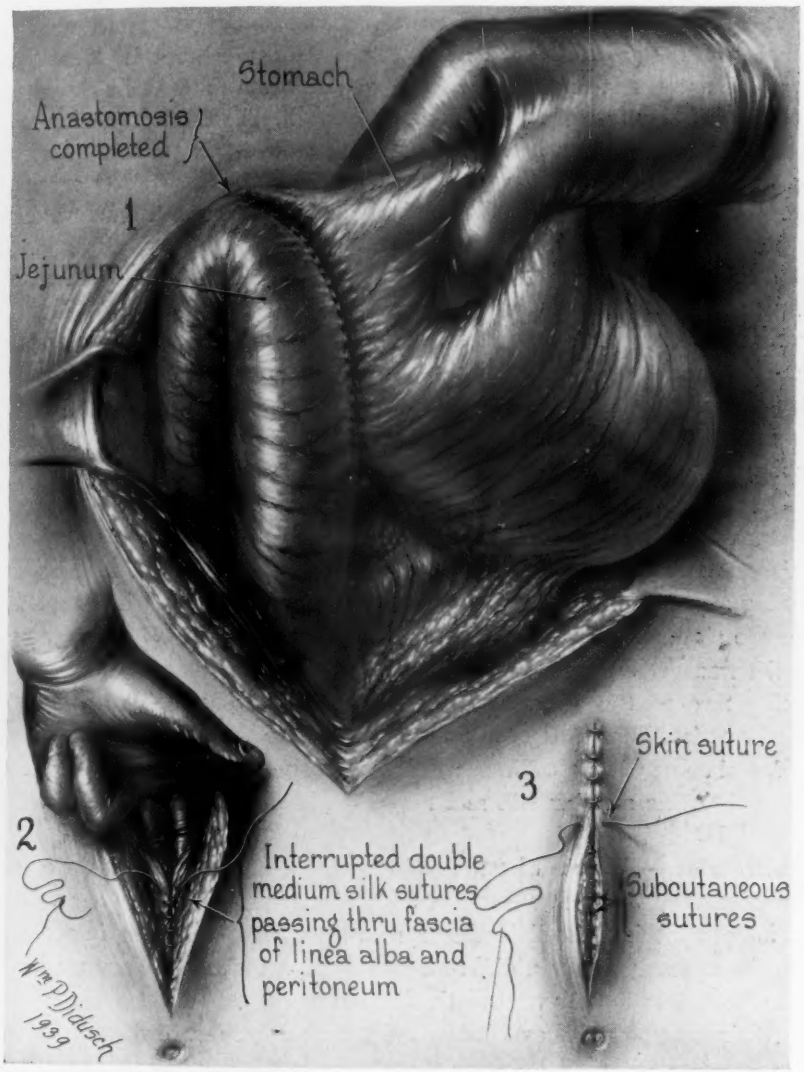

PLATE VII.—Demonstrating the anastomosis completed, the proximal end of the jejunum to the lesser curvature of the stomach in Figure 1; closure of the abdominal wall with interrupted medium silk in Figure 2, and the skin in Figure 3. No stay sutures used.

only three fingers' breadth. A few centimeters proximal to the Payr crushing clamp, a noncrushing clamp is placed upon the stomach and a similar one upon the jejunum. Gauze webbing is used to cover the blades of the noncrushing intestinal clamps in preference to rubber, the former having the advantage of

being far less bulky and affording much greater purchase, and therefore, capacity to hold with less pressure exerted on the tissue through the blades of the clamp. The Payr crushing clamp is then removed and mucosa clips are placed upon the cut end of the stomach embracing only the crushed portion of the stomach wall, while the imprint of the Payr clamp is plainly visible (Plate VI). Halsted interrupted fine silk sutures are then inserted about 0.5 cm. apart, as the posterior suture line. The entire suture line is placed before any of the sutures are tied, thus allowing more room for inserting successive sutures accurately than if they are tied as placed. The crushed portion of the stomach wall, which has been grasped by the mucosa clips, is then excised. The posterior interrupted suture line is much more easily and accurately placed if the mucosa clips are allowed to remain on through this step in the operation. This is due to the fact that the clips, lying in such a manner that their handles point to the left, cause the posterior wall of the stomach to be thrown anteriorly and place it in a more convenient position for suturing. The jejunum is then opened and a continuous suture of No. 1 chromic catgut is placed as an internal suture line in both the posterior and anterior lips of the mucosa. These stitches are locked only at the ends, to prevent any chance of diminution of the stoma by constriction. The final anterior row of Halsted interrupted "a" silk sutures is placed in position before the noncrushing intestinal clamps are removed, but they are not tied. This is accomplished after the stomach and intestine have been released from the noncrushing clamps. In this manner the sutures are more accurately placed and then tied without exerting any tension on the wall of the viscera. A couple of interrupted sutures are placed between the lateral wall of the proximal loop of the jejunum and the transverse mesocolon to prevent a loop of jejunum lower down from slipping through this potential opening. The anastomoses have so far been made isoperistaltic with the proximal loop sewn to the lesser curvature.

The abdomen is closed in the following manner: The linea alba with interrupted double medium silk and the skin with interrupted fine silk sutures (Plate VII).

Discussion.—The use of combined anesthesia is not new, but the employment of a very light nitrous oxide and oxygen analgesia together with the creation of a block of the abdominal sympathetic nervous system, in operations upon the stomach, forms a different combination than heretofore used. The inevitable fall in blood pressure that occurs when only local and splanchnic anesthesia is employed is avoided by the stimulating effect of the nitrous oxide and oxygen. Entirely aside from the anesthetic effects of local infiltration, in and about the celiac sympathetic plexus, is the resultant block in this nervous pathway both to and from the stomach and small intestine. It would seem that the interruption of efferent impulses from the operative field to the higher centers may play an important rôle in the prevention of operative as well as postoperative shock. Regardless of the length of time occupied by the operative procedure, there has been no instance of shock during or after the opera-

tion in any one of this series of 38 patients. In fact, no elevation of the pulse rate or fall in blood pressure has occurred either during or after the operation. Relaxation of the abdomen during the operation is fully as complete, if not more so, than with a general anesthetic. However, even more striking is the uncomplicated smoothness of the immediate postoperative period of convalescence, the first four or five days, of those patients in whom the sympathetic block anesthesia has been made, compared to those who have been given a general anesthesia. The patients in which sympathetic nerve block has been used were almost entirely free from nausea, vomiting, distention and meteorism encountered in the comparative series of cases similarly operated upon, but in which general anesthesia of one type or another was employed. In the latter group the hospitalization was uniformly longer and in many instances this was undoubtedly due to the debilitating effect of a not fatal but severe pulmonary infection or metabolic disturbance pursuant to the inability of the patient to resume his normal fluid intake immediately after operation. It is believed that the sympathetic nerves to the stomach and small intestine provide mainly the inhibiting fibers that give rise to positive dilatation or relaxation preceding a contraction wave, the impulse for which comes largely through the vagi. In a few cases of intractable bronchial asthma in which the thoracic trunk of the vagus nerve was interfered with, there resulted a most severe or obstinate distention of the highest degree. It is likewise felt that the temporary removal of or interference with the function of the sympathetic nerve impulses thus has a tendency to prevent distention, meteorism and stasis by procuring in this manner an unantagonized vagotomic effect. Resection of the pyloric antrum for peptic ulcer of this structure or the duodenum is felt to be desirable because:

(1) From fluoroscopic observations the pyloric antrum or "pyloric mill" is the most active portion of the stomach from the standpoint of tonic and peristaltic contraction. That such muscular activity in the gastro-intestinal tract is productive of symptoms even in the absence of ulcer is a well known clinical fact.

(2) Recent physiologic observations have established, beyond peradventure, that the chemically stimulated gastric secretion, in contradistinction to the psychic secretion, is more prolonged than the latter and results from the secretory activating influence of a hormone, "gastrin." The latter is produced almost entirely in the mucous membrane of the pyloric antrum. The total ablation of this portion of the stomach removes from the secretory chain one of the major links in the secretory mechanism. The proof of this assertion is to be found in the follow-up examination of these patients. Over 85 per cent of them have been examined. In each of these, a plain, in some, an alcohol, test meal has been employed. In two patients only has there been a persistence of a high free and combined acid, but both of these are symptom free and perfectly well. In the remainder examined there has been either no free hydrochloric acid or a very small amount with a low combined acidity. The time elapsing since operation varies from four years to six months, and, so far,

there have been no instances of definitely detectable recurrence of an ulcer or marginal ulcer at the site of the gastro-jejunal anastomosis. Hemorrhage recurred three times in each of two patients following operation. One is at present in the Johns Hopkins Hospital recovering from a severe hemorrhage, the source of which is unknown at present. The other, a medical student, is now well and at work. The source of his postoperative hemorrhage was likewise undetermined. Fluoroscopic examination of these postoperative stomachs has shown the emptying time to be slightly faster than normal.

(3) The remaining portion of the second part of the duodenum is placed at rest by shunting food and gastric secretion away from this potentially ulcer bearing area.

From the technical side, the short-loop, antecolic gastrojejunostomy has these points to recommend it:

(1) It is probably the simplest of gastric resections to perform, and is apparently efficacious.

(2) The mortality is much less than in the more extensive resection and the ultimate postoperative results are equally as good.

(3) If further operative procedures should prove necessary, more stomach remains to operate upon.

(4) The antecolic is to be preferred to the retrocolic anastomosis because the proximal loop of jejunum is just as short in the former as in the latter. Further, the complications that not infrequently are precipitated by the mesocolon are thus avoided.

(5) With such a short proximal loop in the jejunum, an entero-enterostomy is unnecessary. The length of jejunum from Treitz's ligament to the beginning of the anastomosis is not over three fingers' breadth.

(6) The removal of devitalized tissue by the crushing clamp enhances primary healing of the suture lines.

(7) Attention is called to the continuous suture distal to the small Payr crushing clamp on the duodenum. This suture line is placed in viable tissue beyond the clamp so that when the crushing clamp is removed and the crushed tissue trimmed away, the subsequent inverting Halsted interrupted sutures turn in only healthy tissue. In other methods of sutures, such as the Parker-Kerr, there remains a line of clamped necrotic tissue in an infected blind pouch. It would seem better to remove this tissue.

CONCLUSIONS

(1) A combination anesthesia consisting of sympathetic nerve block with a light nitrous oxide and oxygen analgesia has given excellent results in resection of the stomach.

(2) Resection of the pyloric antrum or "pacemaker" of the stomach combines the attributes of simplicity and safety as well as the restoration of the production of gastric secretion to approximately normal.

(3) Extensive resections of the stomach are far more hazardous and no more efficacious in the great majority of cases.

(4) Thus minimal resection of the stomach, removing only the pyloric antrum, is a rational procedure based on known anatomic and physiologic data; and from the standpoint of immediate and postoperative results is sufficiently radical to restore the patient to a normal state of health in the great majority of instances.

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DISCUSSION.—DR. HARVEY B. STONE (Baltimore): All of my own cases in the group which Doctor Rienhoff has reported were operated upon under general anesthesia. I did not employ splanchnic block in any of my cases, and two of the three pneumonia deaths were among my own patients.

It is largely a matter of speculation, of course, as to what might have been the result in these particular patients had they been operated upon under splanchnic block rather than inhalation anesthesia, but for the sake of his presentation, I wish to acknowledge very frankly that the pneumonias were all in the group receiving inhalation anesthesia.

I think there is nothing more that I have to add except to say that I have been impressed with the ease and safety of the limited resection with an antecolic Pólya type repair without the addition of an entero-enterostomy. It certainly is a much simpler and less hazardous procedure than the more extensive resection.

On three occasions, I have resected small carcinomata in the pyloric region of the stomach under simple abdominal wall infiltration anesthesia without either general inhalation or nerve block, and without any evidence of particular distress on the part of the patient.

DR. J. SHELTON HORSLEY (Richmond, Va.): The method of anesthesia that Doctor Rienhoff has so well described is excellent, particularly in patients who are bad risks and who are elderly. I have not infrequently found that a partial gastrectomy after that type of anesthesia will result in the patient's leaving the table with practically the same pulse rate, and almost the same blood pressure, as he had when he came in. If it has any tendency to fall, the blood pressure is kept up by intravenous dextrose and Ringer's solution.

The excision of the pyloric end of the stomach does take away, as Doctor Rienhoff has said, a kind of hormone which Edkins described, in 1906, as being produced in the pyloric portion of the stomach. It seems to activate the rest of the stomach. The pyloric end of the stomach, however, secretes alkaline material and not acid. Resection of one-half or two-thirds of the stomach, does undoubtedly remove much of the acid-bearing portion of the stomach and,

therefore, decreases the manufacture of acid for a while but probably not permanently. For instance, if one reasonably healthy kidney is removed as the result of trauma, there may be some temporary strain upon the other kidney, but sooner or later the other kidney takes up the whole function and carries on just as well as if there were two kidneys. Similarly, sooner or later, after an extensive gastrectomy, the rest of the stomach doubtless secretes as much acid as the whole stomach did before.

Doctor Rienhoff, as is his habit, presented this so well, and his pictures are so beautiful, that it would seem almost brutal to say a word of adverse criticism, and yet I cannot refrain from remarking two or three things. One is that a Billroth I type of operation, as I tried to demonstrate this morning, preserves the physiologic function more nearly than the Billroth II type. The sensitivity of the intestinal mucosa to acid increases below the duodenum. Two or three feet below the origin of the jejunum is a region of bowel that is much more likely to be affected by the acid pouring into it than the duodenum.

The closure of the duodenum not infrequently results in back pressure, and occasionally in a duodenal fistula, which would be difficult if not impossible when the Billroth I modification is performed.

Still another criticism is that when the wound in the pancreas is left after shaving off pancreas with a knife, instead of the cautery—the cautery seals it and makes it sterile and kills some of the infective agents—the pancreas is left exposed and unprotected, whereas, when it is cut with a cautery and the Billroth I modification described this morning, is employed, the stomach is brought over to the stump of the duodenum, united in a physiologic way, and the wounded surface of the pancreas is covered by the posterior wall of the stomach.

Dr. Frank H. Lahey (Boston): After having had a fatality from a cyclopropane explosion, we interested the Massachusetts Institute of Technology in trying to find out what caused the explosion and to develop something which will probably diminish the likelihood of such explosions. This is only one thing toward reducing explosion hazards, but I would feel wrong if I went home without presenting the plan of this intercoupler which has been devised.

This work has been done by Professor J. W. Horton, Professor of Biological Engineering at the Massachusetts Institute of Technology, in cooperation with the members of the Department of Anesthesia of the clinic.

This intercoupler unit provides a means for electrically intercoupling the patient, the anesthetist, the machine, and the operating table. It thus keeps them all at the same electrical potential. Its purpose is to eliminate static spark between any two of these bodies and thus reduce the hazard of igniting explosive anesthetic agents. You all know the value of ordinary intercoupling in reducing static. This is, however, a new type of intercoupler. It has five segments to it, and each segment has in it a resistance of one million ohms, that is, one megohm. This resistance of one million ohms is introduced into the connection between each pair of intercoupled bodies, making it possible to intercouple five units—table, anesthetist, apparatus, anything else; five individuals can be intercoupled with a resistance of one million ohms between each one. In this way certain risks which would accompany direct intercoupling by ordinary chains or wires are avoided. Any current from the lighting circuit which might accidentally pass to the patient or anesthetist through the intercoupling connection is limited to magnitudes which are not dangerous.

The intercoupled bodies are also prevented (this is the important development, I think) from acting as a single electrostatic condenser of high capacity.

This is desirable in order not to increase the energy in any sparks which may be received from unintercoupled bodies. It must be emphasized that the sole function of the intercoupler is to equalize electrostatic potentials between such bodies as may be directly connected to it. It provides no immunity from electrostatic discharges from other bodies. Its use does not justify the neglect of any other possible precaution against electrostatic sparks or against other agents which may ignite inflammable gases.

We do not sell it; we are not interested in it. It is built by the hospital. It costs but $7.50. It is very definitely a method by which sparks built up in a unit, which is part of the operation, can be reduced to such a degree of heat that they will not ignite inflammable gases. This is of particular importance, since most of the explosions will occur from leakages about the face mask or from within the apparatus itself.

I do not think this is the complete answer to the prevention of explosions. It is, however, a distinct aid in preventing explosions from their common cause, that is, charges built up within individuals or within apparatus and the production of static sparks particularly close to the mouthpiece.

DR. ROSCOE GRAHAM (Toronto, Canada): I should like to present certain facts in regard to our impressions of spinal anesthesia in abdominal surgery. Conflicting reports, conflicting enthusiasms, and the unfortunate sequelae that have been reported would seem sufficient to condemn spinal anesthesia. Despite the fact that these reports have been published, the preference of our staff for spinal anesthesia in upper abdominal lesions is represented by 144 instances in 158 recent upper abdominal operations.

I think that the conflict of practice and report is probably due to the fact that many statements are passed on without substantiation. Doctor Foss' case is an excellent example of where an entirely irrelevant lesion is blamed on the anesthetic. We believe that the adequate operation which can be performed under spinal anesthesia is a great advance. Your experience may be at variance with ours, but in the question of common bile duct lesions, prior to January, 1934, we never did find more than a 10 per cent occurrence of stones in the common bile duct in conjunction with cholelithiasis. There was a reason. We opened the common bile duct only in cases where it was obviously impaired, because the trauma, resultant morbidity, and the disturbed convalescence deterred us.

Our interest in modifying the ordinary inhalation anesthesia started in 1926. At this time, we adopted splanchnic block through the open abdomen as advocated by Doctor Finsterer and presented to you to-day by Doctor Rienhoff. I think it was good for the patient. It was hard on the surgeon, and in 1930, we supplanted this by the use of spinal anesthesia.

In the last 311 cases of cholelithiasis, we have explored the common duct in 46 per cent of cases and we have removed stones in 21 per cent. That is a sad comment on our ability as surgeons previously, but it is an excellent commendation of our belief that with the relaxation of spinal anesthesia in these complicated and difficult intraperitoneal operations, we can carry out this type of operative and technical procedure with full confidence that that procedure is not adding to the mortality and morbidity. Furthermore, we believe that the conflict of opinion and practice with regard to spinal anesthesia is due to three factors: First, the choice of the anesthetic agent; and second, the anesthetist. We have never used an anesthetic agent that was not dependent for the height of anesthesia on the volume of fluid injected. We use procaine or novocain, either in crystal form or in solution, or nupercain in 1:1,500 dilution.

We have never had a serious neurologic lesion. We had one which was discovered only on the day following operation, and that was the paresis of the external rectus muscle of the eye. It seems difficult to understand that such could be due to the spinal anesthesia, but it has been reported by others. It cleared entirely in three weeks.

The third important factor we believe is the method and the technic of administration. We most heartily must condemn the surgeon who is his own anesthetist and uses spinal anesthesia. We believe that spinal anesthesia, unless administered and supervised by a skillful and adequately trained anesthetist, is a dangerous anesthetic. We believe that we must correct biochemical faults and fluid imbalance before administering spinal anesthesia. We further believe that the use of small needles, No. 22 gauge, is of importance in preventing postoperative spinal headaches. In addition, the elevation of the foot of the bed ten inches for ten hours and the intravenous administration by the drip method of 1,500 to 2,000 cc. of saline postoperatively we believe is of importance in preventing spinal headache.

The freedom from complications with spinal anesthesia is outstanding in our experience when compared with a similar group of operations carried out under inhalation anesthesia.

Many of the condemnations of spinal anesthesia are because it is not of sufficient duration to permit prolonged and complicated intraperitoneal operations. That is true, technically, in the cases such as were described this morning of the gastrojejunocolic fistulae which are particularly difficult and require prolonged procedures.

The supplemental inhalation anesthesia, particularly if the patient has been given adequate preoperative sedation, we feel is accompanied by real handicap. We had one patient who died, we believe, of anoxemia and fulfilled the requirements which Doctor McClure and Doctor Hartman presented. The patient had been given major sedation previous to operation, and that had been supplemented during the operation by intravenous sodium amytal to control the nausea. Following the supplemental inhalation anesthesia, the patient developed apnea for some time, with the resultant anoxia. The patient died seven hours later.

If the duration of the operative procedure is such that it is likely to require supplemental anesthesia, we do not give excessive sedation, and we do not supplement with deep inhalation anesthesia, but anticipating the diminution of the efficacy of our spinal anesthesia, we use splanchnic block at this time coupled with field block. That has been most efficacious, and I would only ask, in conclusion, that we recognize the limitations of spinal anesthesia; that we recognize it as a dangerous anesthesia unless there is adequate preparation, skillful support, supervision and administration of the anesthesia; that we hesitate to pass on criticisms and statements of sequelae without first substantiating them by fact.

DR. FRASER B. GURD (Montreal, Canada): I feel that it is necessary, or at least advisable, on my part to indicate the reason why, three years ago, we were induced to commence the employment of spinal anesthesia for thoracoplasty in the treatment of pulmonary tuberculosis.

About 50 years ago, there was established in Montreal the Grace Dart Home. The establishment of this home was in order that cases about to die from pulmonary tuberculosis could be, in the first place, removed from their homes, and in the second place, made as comfortable as possible. In 1932, a hospital was built to replace the home. Nevertheless, the traditions of the old Grace Dart Home continued, and to the new hospital was admitted, in large

measure, the same type of cases. An operating room had been provided in the new hospital, and, in 1933, I was asked to organize a surgical staff for the purpose of employing surgical therapy in the treatment of the cases.

Our medical staff, that is, the physicians proper, put the matter up to me in this way, stating that: "We are all familiar with the results of thoracoplasty in the properly selected cases according to Doctor Archibald's good, chronic type. Will you be willing to undertake surgical interference in the type of cases we have in this hospital in order to discover whether these cases, or some of these cases, who appear to be destined to early exitus cannot have the course of the disease arrested?"

Having worked for three years in France at a Clearing Station, and having under those conditions had thousands of young men die under my care, I replied that I was quite prepared to carry out such a form of treatment.

During the first two or three years (the service, by the way, is not a large one), there were 27 cases operated upon, that is, about 100 operations. We employed all forms of anesthesia and all mixtures of anesthetics, including cyclopropane, evipal, avertin, ether, nitrous oxide, and various forms of preoperative sedation. Of the 27 cases operated upon prior to July, 1936, we had seven deaths within six weeks of operation, that is, we had seven which we considered postoperative deaths. I felt it was necessary, having such a mortality rate, to state my apologia before stating the figures.

Four of those deaths were frankly due to bronchial spreads of the disease, and the postoperative institution of an acute pneumonic phthisis. In addition, there were eight other cases in which extensive and marked bronchial spreads occurred. Those patients ultimately died, and more quickly, we are sure, than had they not been operated upon.

We were depressed, and spoke to Doctor Bourne, who has spoken to us here this afternoon, and asked him whether he thought we could try some other method, especially spinal anesthesia, in the hope that in this particular type of case we might be able to improve our results.

I am going to state the matter very briefly from here, gentlemen. Since July, 1936, we have operated upon 42 cases, 24 of whom were bilateral. We have had two deaths in the operating room. We have had three commotions, I would call them, that is, in three cases we were disturbed in the operating room by the condition of the patient. The patients, however, afterwards did well. There have been three minor spreads. We have had no deaths other than the two in the operating room during the first two months following operation.

Of those 42 cases, 37 were extrapleural thoracoplasties, usually three-stage, commencing with the third, second and first ribs, and five were the production of extrapleural pneumothoraces which, as you know, necessitates, among other things, the dissection of the extrafascial plane of the thorax from the brachial plexus and the subclavian vessels.

In no case have we had to supplement with any other anesthetic. In no case has there been any complaint or special apprehension on the part of the patient who had to undergo a second and then a third operative procedure. In but two cases have we deemed it expedient to employ blood transfusion, although as a matter of fact we are in a position to employ blood transfusions easily, but we have not thought it necessary.

We have employed the Etherington-Wilson technic, which is that, in the erect posture, from 12 to 13 cc. of nupercain (1:1,500) is introduced between the second and third lumbar interspace. The back of the patient has been estimated as being long, short or medium in length. We have, or rather Doctor Bourne has, following the commencement of the introduction of the

hypotonic, that is, hypotonic as compared to the cerebrospinal fluid, started the stop-watch, and from 50 to 55 seconds has been the length of time which we have deemed was the proper length of time to reach the sixth cervical region, approximately.

That, briefly, gentlemen, is our statement. As I said in the first place, we explained as to why we felt justified in carrying out the experiment. Our experiment, if such it may be called, and I think it can be properly called so, is justified by our results, and in any event it proves quite conclusively that with comparative safety, and with certain satisfaction to both surgeon and the patient, the first rib together with its transverse process may be removed in its entirety, and as I have already pointed out, that necessitates the displacement of the whole of the brachial plexus, since we make it a practice to carry out substantially Semb's procedure without undue mortality. We are not certain why the two patients died in the operating room. We are prepared to admit that they were due to our form of anesthesia, although that is not positively certain in our own minds.

DR. ERWIN R. SCHMIDT (Madison, Wis.): The discussion this afternoon has raised certain questions in my mind. In the discussion on anoxia, I am not worried so much about the people that died, because they are evidently taken care of, but I am wondering about the many people who have been crippled by different degrees of anoxia of which we know very little. It certainly is a subject over which we as surgeons should very carefully cogitate.

With reference to the explosions, having been one of the individuals who helped bring cyclopropane into the surgical field, there are certain questions that come up in my mind. In the first place, several years have elapsed, and cyclopropane has been used, and it is only recently that the explosions have happened. That is one question.

Then, as far as the statistics are concerned, I do not believe much in statistics any more. At the present time we are getting some reports of explosions, but as far as I know, ever since the discovery of anesthesia—ether and chloroform—we have had several agents at our disposal, and of all the agents, only local and chloroform are nonexplosive agents. It is my personal opinion that we know very little of what is happening in the field of anesthesia, because only within the last few years have we had people who knew something about anesthesia, and these individuals are interested in reporting what they have found, a real search after the truth. Before this time, I have a feeling that a great many explosions are buried in the memories of men.

We come to realize that there are many agents, and it seems to me as surgeons we have to realize that it requires a great deal of knowledge in many different ways in order to bring the information which we have to focus on the problems we have with each individual patient. I agree very heartily with Doctor Graham, when he discussed spinal anesthesia, that it is only within the last few years that we are really obtaining some evidence that we can depend upon in determining the clinical course, or the things we want to do with patients as far as anesthesia is concerned.

Now, it seems to me that viewing this with a general, broad viewpoint, it sums itself up something like this: What may be a good anesthesia in my hospital is not a good anesthesia in your hospital, and if we recognize that and use some common sense in the agents that we employ, so that in each individual place the agent, whatever it may be, is the best one that can be employed in that individual place, then I think we will find a great improvement in our anesthesia, and I believe that the enthusiasm, the work and the science that have been applied by this small group of individuals, are going to amplify the art which has been practiced so many years in surgery and anesthesia.

THE SIGNIFICANCE OF LIPOCAIC IN SURGERY*†

LESTER R. DRAGSTEDT, M.D., PH.D., DWIGHT E. CLARK, M.D.

AND

C. VERMEULEN, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY OF THE UNIVERSITY OF CHICAGO, CHICAGO, ILL.

TWO YEARS after the isolation of insulin by Banting and Best,[1] in 1922, it was discovered by Fisher[2] and by Allan, Bowie, Macleod, and Robinson[3] that completely depancreatized dogs could not be kept alive for long, even though adequately treated with the new hormone. Death usually took place within two or three months. At autopsy, the liver was found to be markedly enlarged and its parenchyma almost entirely replaced by fat (Figs. 1 and 2). The addition of raw pancreas to the diet was found by Macleod and his associates to prevent the development of these liver changes and to permit survival for long periods of time. These findings have been repeatedly confirmed. In 1930, Hershey,[4] and, in 1931, Hershey and Soskin,[5] reported that the addition of 10 Gm. of lecithin daily to the diet of the depancreatized dog treated with insulin was also effective in preventing the characteristic liver damage and in permitting survival. The active constituent in this effect was found by Best and Huntsman,[6] and Best, Ferguson, and Hershey[7] to be choline.

The depancreatized animal suffers from two obvious deficiencies—insulin and pancreatic juice. The fact that insulin, together with an adequate, balanced diet, does not suffice to permit such animals to survive in good health suggested that the pancreatic secretion might also be necessary. In fact, it was this possibility that led Macleod and his associates to investigate the effect of feeding raw pancreas as a source of the pancreatic enzymes. The discovery that lecithin and choline were, at least to some extent, effective in preventing the liver changes in depancreatized dogs cast doubt on the assumption that pancreatic juice or certain of its constituents were necessary, and it was perhaps fairly generally believed that the beneficial effect of pancreas feeding was due to its content of lecithin and choline.

During the past four years, a considerable amount of evidence has been accumulated in our laboratory[8, 9, 10] which indicates that neither of these assumptions is correct. On the other hand, the conclusion seems inescapable that the pancreas manufactures a second internal secretion, apart from insulin,

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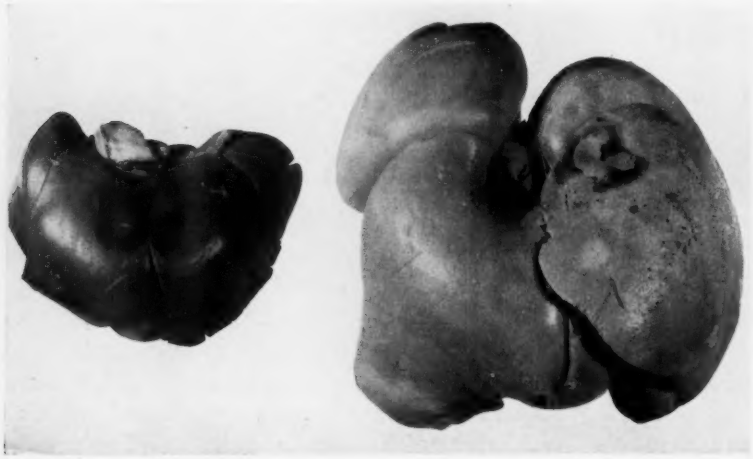
which plays an important and perhaps vital rôle in metabolism. This evidence may be in part summarized as follows:

(a) The failure of the insulin treated depancreatized dog to survive is



(a) (b)

FIG. 1.—(a) Photograph of normal liver of dog. (b) Photograph of the liver of an animal of approximately the same size, that had been depancreatized and preserved as long as possible by the administration of insulin. Death occurred after 60 days and, at autopsy, the liver was found to be enlarged and bright yellow in color.

not due to the absence of pancreatic juice or its constituent enzymes, since animals with complete pancreatic fistulae may survive indefinitely if deminer-

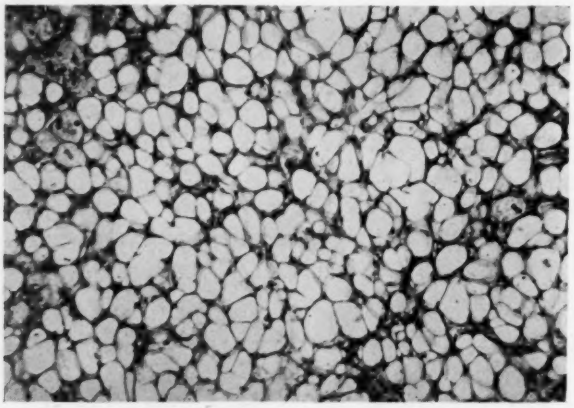


FIG. 2.—Photomicrograph showing the marked fatty infiltration of the liver in a depancreatized dog fed a balanced diet and treated adequately with insulin. Death occurred 60 days after pancreatectomy.

alization and the development of ulcers in the stomach and duodenum are prevented.[11, 12, 8] Such animals do not develop the fatty changes in the liver which appear in insulin treated depancreatized dogs. Furthermore, the oral administration of fresh active pancreatic juice does not prevent the development of fatty infiltration of the liver in depancreatized dogs nor prolong life.

As a matter of fact, the fatty infiltration occurred somewhat sooner and was more marked in these animals than in the control group that received no pancreatic juice. This is probably to be attributed to the better digestion and absorption of fat in the former case.

(b) The beneficial effect of pancreas feeding in preventing the fatty infiltration of the liver in insulin treated depancreatized dogs is not due to its content of lecithin or choline, since liver and brain, which contain even more of these substances, have no such beneficial effect.[8] If depancreatized dogs are fed a mixed diet of protein, carbohydrate, and fat and the diabetes is well controlled by insulin, it requires at least 2.0 Gm. of choline over and above that which is present in the food in order to prevent the characteristic fatty changes in the liver. One hundred Gm. of fresh pancreas, which is an adequate preventive or curative dose, contains only 232 mg. of choline.[13]

(c) It has been possible to prepare extracts of pancreas that are entirely free from lecithin and practically free of choline and which are just as effective as raw pancreas in preventing or curing the fatty changes in the livers of depancreatized dogs and in permitting these animals to survive. The details of the method of extraction will be presented elsewhere. It may be stated here that fresh beef pancreas is first thoroughly extracted with neutral alcohol. The filtrate may then be evaporated to dryness and extracted with ether. The ether extract contains the fat of the pancreas and hence practically all the lecithin and choline, but has no therapeutic value. The fat-free alcohol extract is, however, effective on oral administration in amounts of from 1 to 2 Gm. per day in preventing and curing fatty infiltration of the liver in depancreatized dogs. Figure 3, a, b, c, d, e and f, illustrates the improvement in the histologic appearance of the liver brought about by this material. This fat-free alcohol extract may be further concentrated and purified by dissolving it in water and then precipitating it out by saturation with ammonium sulphate. The precipitate may be then dissolved in glacial acetic acid. The addition of ether to the glacial acetic acid throws out a precipitate which has been found to be active by both oral and subcutaneous administration in amounts of less than 150 mg. per day. This product contains no fat and is free of appreciable amounts of choline.

The demonstration that a second internal secretion is normally provided by the pancreas depends upon the recognition that the depancreatized dog, fed upon a mixed diet of protein, carbohydrate, and fat, is not restored to a normal state by the adequate administration of insulin and pancreatic juice, and that the remaining deficiency can be corrected by the oral administration of pancreas or of certain extracts of pancreas, but not by other organs. We have suggested the name "lipocaic" for this hormone. This is derived from the Greek and suggests in a general way the oxidation of fat. The function of this internal secretion is still very little understood. The sequence of events which commonly follows when a dog is pancreatectomized and thus deprived of pancreatic secretion, insulin and lipocaic is as follows: Hyperglycemia, hyperlipemia, glycosuria, disturbance in digestion, increasing ema-

FIG. 3.—Illustrates the improvement in the histologic appearance of the liver produced by the oral administration of lipocaic. (a) Dog 665: Biopsy showing extensive fatty infiltration in the liver ten weeks after pancreatectomy. Liver function test showed 20 per cent retention of bromsulphalein 20 minutes after injection of the dye. (b) Dog 665: Biopsy of liver after oral administration of 1.0 Gm. of fat free alcohol extract of pancreas daily for two weeks. There is no decrease in fat but the liver function test was now normal. (c) Dog 665: Biopsy of liver after oral administration of lipocaic for four weeks. There is some decrease in fat and a small island of normal liver tissue. Liver function normal. (d) Dog 665: Biopsy of liver after oral administration of lipocaic for six weeks. There is still more decrease in the liver fat. (e) Dog 665: Biopsy of liver after twelve weeks of lipocaic therapy, showing marked improvement. (f) Dog 665: Biopsy of liver after 12 weeks of lipocaic therapy, showing almost complete return of normal structure.

ciation, and death from so-called pancreatic diabetes in one to four weeks. If this depancreatized animal be placed on a mixed diet of protein, carbohydrate, and fat, given active pancreatic juice by mouth, and sufficient insulin (usually 10 to 20 units) to limit the excretion of urinary sugar to about 10 Gm. per day, life is considerably prolonged and the defect due to the absence of lipocaic made manifest.

There occurs a steadily lessening excretion of glucose in spite of continually decreasing doses of insulin, until after five or six weeks the animal may excrete only a gram or two of glucose per day and receive only two or three units of insulin. Larger amounts, even five units, may at this time provoke fatal hypoglycemic convulsions. Superficially, it might appear as though the animal were recovering from the diabetes. However, certain definite abnormalities are present. The blood fats are reduced to approximately one-half of the normal concentration and tests reveal defective liver function. An abnormal retention of bromsulphalein[14] is commonly found. Whereas digestion and absorption are improved by the administration of pancreatic juice, the animal becomes progressively weaker and emaciated and death occurs. At autopsy the liver is found to be enlarged to three or four times its normal size and so infiltrated with fat that its normal architecture is entirely obscured. Of 154 depancreatized dogs, whose course was carefully studied in our laboratory, only 13 failed to develop these fatty changes. Both regular and protamine-zinc insulin have been used in this work and no significant difference observed.

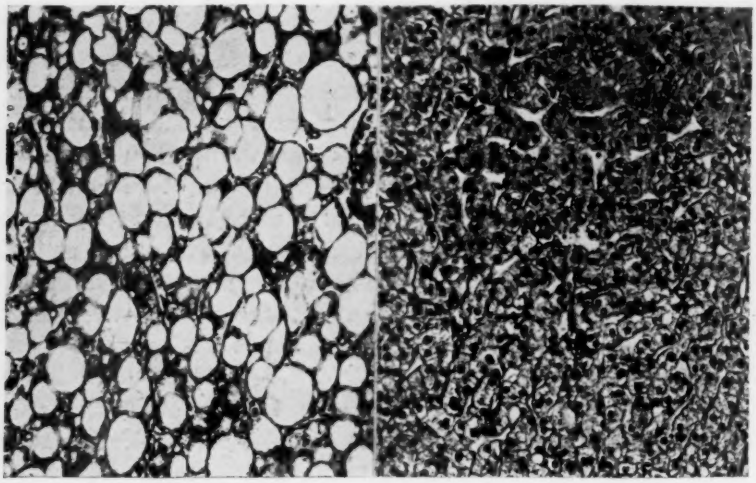
If lipocaic be given to such a depancreatized animal at the time when the sugar excretion has become minimal, the insulin requirement reduced, the liver function impaired, and the concentration of blood fats decreased, a striking change is produced. The blood lipids increase to normal or greater than normal values, an immediate and large excretion of glucose in the urine occurs, and the insulin dosage may be raised to 20 or 25 units per day without harm. Liver function returns to normal within two or three weeks and occasionally sooner. Biopsies of the liver during this period disclose a rapid disappearance of the fat and a return of the normal structure. The large glucose excretion and increased tolerance to insulin suggest that under the influence of lipocaic the fat in the liver is being converted into glucose. The possibility of such conversion in the organism has long been recognized for the glycerol part of the fat molecule, but denied for the fatty acid. The very large amounts of glucose made available in these experiments seem to demand such a conversion for the fatty acid. The general condition of the animal, its weight, strength, and appetite steadily improve under lipocaic administration, and the diabetes reaches a steady state without fluctuations in glucose excretion or insulin requirement. The subsequent withdrawal of lipocaic again produces the characteristic symptoms and findings, which may be again relieved by lipocaic, and this process often repeated.

It seems likely that clinical application of these findings on the lower animals will be obtained chiefly in medicine. There is considerable evidence

(f) Dog 665: Biopsy of liver after 12 weeks of lipocaic therapy, showing almost complete return of normal structure.

at present which indicates that some patients with diabetes mellitus are not returned to an entirely normal state by the administration of insulin. A lessened capacity to utilize fats is often present and some students of this disease have advocated a low fat, high carbohydrate diet plus insulin in treatment. Enlargement of the liver due to extensive fatty infiltration has been reported and several of these cases have responded favorably to lipocaic administration.

Grayzel and Radwin[15] treated three young diabetics with hepatomegaly by means of lipocaic and secured a striking recession of the liver to its normal size. When the lipocaic was discontinued, the hepatomegaly returned and again receded when lipocaic was resumed. The diabetes in these pa-



(a) (b)

FIG. 4.—(a) Biopsy showing marked fatty metamorphosis of the liver in Rosenberg's case. (b) Second biopsy showing the marked improvement in the liver produced by the oral administration of lipocaic.

tients had been well controlled by diet and insulin. The case reported by Rosenberg[16] is of special significance, since it was possible to verify the diagnosis of fatty metamorphosis of the liver at operation and to secure a biopsy specimen, and again to verify the improvement brought about by lipocaic at a second operation. The case was that of a woman, age 59, with mild diabetes, hepatomegaly, and laboratory evidence of impaired liver function. Celiotomy was performed for the removal of an ovarian tumor and at this time the liver was found to be enlarged and grossly fatty. Figure 4a, obtained through the courtesy of Doctor Rosenberg, illustrates the almost complete replacement of the hepatic parenchyma by fat. Lipocaic was then administered orally for a period of 11 weeks, during which time there was marked subjective improvement, decrease in the size of the liver, and improvement in its function as determined by the bromsulphalein and hippuric acid tests. An attack of biliary colic during the twelfth week necessitated a second operation and at this time the author reported a remarkable change in the size and appearance of the liver, which was now normal. A second

biopsy (Fig. 4b) revealed a complete disappearance of the fat and return of the normal histologic structure.

The surgeon will perhaps see cases of fatty metamorphosis of the liver due to lipocaic deficiency where the pancreas has been extensively destroyed following attacks of acute pancreatitis or pancreatic necrosis or where the pancreas has been extensively removed in the treatment of malignant disease. We are indebted to Dr. Warren Cole for Figure 5, which illustrates the extreme fatty metamorphosis in the liver in a patient who, at autopsy, displayed an almost complete destruction of the pancreas, probably as a result of repeated attacks of acute pancreatitis. The development by Whipple, Parsons, and Mullins[17] of a technic for extirpation of carcinoma of the ampulla and

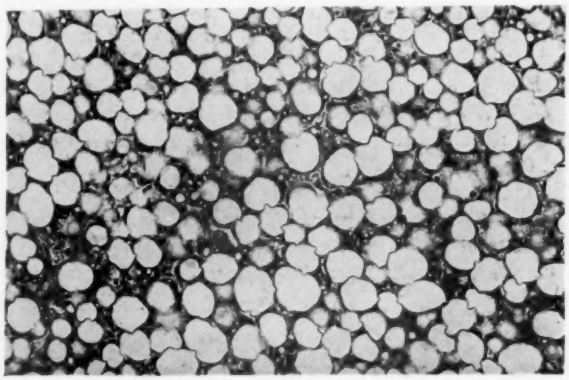


FIG. 5.—Photomicrograph showing the extensive fatty metamorphosis of the liver in Warren Cole's case.

of the pancreas seems destined to become increasingly successful, and we will doubtless see more and more long-time survivals following such operations. We have no reason to believe that the response of man to pancreatectomy will be different from that in the dog. In that case, it seems important to recognize that the absence of pancreatic juice from the intestine is relatively unimportant, leading only to a partial impairment in digestion and absorption, whereas the deficiency in the internal secretions, insulin and lipocaic, is incompatible with life.

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DISCUSSION.—DR. J. SHELTON HORSLEY (Richmond, Va.): This is a remarkably interesting paper, not only for the discovery of an apparently new histogenesis of fatty changes in the liver, but because it opens up several other questions. One, for instance, is that in the so-called fatty degeneration of the liver after certain drugs, such as chloroform, which is a well-known cause of death after chloroform anesthesia, may it not be possible that this fatty degeneration is not due to a direct effect upon the hepatic cells, but to the action upon the pancreas, which in turn produces this fatty degeneration of the liver by a suppression of lipocaic? I should like very much to hear Doctor Dragstedt express his opinion about this.

A quite dramatic thing is the recovery of a liver that seems to be practically all fat. I am wondering if those areas of fat are true fat cells—they can hardly be—or whether it is just an accumulation of fat within the capsule of the cell. It would seem remarkable that a portion of a liver apparently consisting of nothing but fat, like a lipoma, could regenerate so completely under lipocaic, and hepatic cells be built up from what seem masses of fat. There doubtless must be some element of nucleus or something else in the capsule of these fat-like cells that initiates regeneration.

DR. FREDERICK REICHERT (San Francisco): I should like to ask Doctor Dragstedt if he knows whether this second internal secretion of the pancreas is affected by hypophysectomy. As I remember the study of the livers in hypophysectomized young animals, they appeared normal, but I do not recall the appearance of the liver in adult dogs.

DR. LESTER R. DRAGSTEDT (closing): Doctors Bollman and Mann have recently made some significant studies with respect to the nature of the fatty livers which occur following the administration of alcohol. They found that

if dogs were placed on a diet deficient in carbohydrate but rich in fat, and then given alcohol, an extreme fatty infiltration in the liver develops. This fatty infiltration could be relieved by the administration of carbohydrate and also to a certain extent by the administration of lipocaic.

Doctor Horsely's question presents a very interesting suggestion. It is indeed possible that the fatty infiltration of the liver that follows upon the administration of alcohol might well be due to inhibition of the formation of lipocaic by the pancreas. The fat in these cases is in the hepatic rather than the Kuppfer cells. The very large amount of fat present gives the cell a signet-ring appearance. Animals that have survived for long periods of time with only moderate degrees of fatty infiltration display a very marked cirrhosis of the liver.

In answer to Doctor Reichert's question, fatty infiltration in the liver does not regularly develop in the hypophysectomized animal. However, if the hypophysis is removed and then at a subsequent date a total pancreatectomy is performed, a mild type of diabetes develops, as was demonstrated by Houssay, and these animals develop a marked fatty infiltration in the liver, similar to that which occurs in the depancreatized dog. This type of fatty liver in the Houssay dog is also relieved by the administration of lipocaic.

A DISCUSSION OF MULTIPLE NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)*

REPORT OF TWO CASES HAVING UNUSUAL SURGICAL COMPLICATIONS

RANDOLPH JONES, JR., M.D.

AND

DERYL HART, M.D.

DURHAM, N. C.

FROM THE DEPARTMENT OF SURGERY OF THE DUKE UNIVERSITY SCHOOL OF MEDICINE, DURHAM, N. C.

MULTIPLE NEUROFIBROMATOSIS remains a disease of great interest because of the probable familial nature of the affection, the complexity of its morphology, the progressive character of its course, and the numerous complications which may develop during its evolution. Moreover, although von Recklinghausen's disease has been the object of study by many investigators, there is still some lack of agreement in the interpretation of certain of its aspects, and the cause of the disease remains unknown. In this presentation we will make a general survey of the disease, with illustrations of its familial character and many of its clinical manifestations, taken from our own records. Two of our cases with unusual complications, requiring surgical intervention, are reported in detail.

The Familial Character of von Recklinghausen's Disease.—That multiple neurofibromatosis frequently recurs in successive generations of the same family has long been known, but the hereditary character of the disease did not attract widespread attention until 1910.[1] In its hereditary occurrence, it is analogous to multiple telangiectasis,† to tuberous sclerosis, and to polyadenomata of the rectum.[2] Although it is not possible in all cases to demonstrate inheritance of the condition, the percentage of patients having a family history of the disease varies in different reports from 18 to 74 per cent.[3]

It is also of interest to note that similar clinical types of the affection may appear in several individuals of the same or successive generations of a given family,[4] as has been reported in uniovular twins,[5] in a family with intracranial tumors in a high percentage of members through three generations,[6] and in other families showing a high incidence of malignancy.[7]

Numerous instances of the transmission of multiple neurofibromatosis through three generations are on record.[4,8] A number of our patients have given a family history of the disease, and in one we have been able to trace it through four generations while the members of the fifth are too young as yet to show definite signs of involvement (Chart 1). Although there is some doubt that the hereditary factor is transmitted as a mendelian dominant, such

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

† Hemangiomatosis is mentioned also as an hereditary disease affecting the central nervous system.[8]

seems to have been the case in a number of families which were followed for more than two generations,[4, 9, 10] and this view is supported by the family tree shown in Chart 1. That the inheritance is not sex linked, is also borne out by this family (Chart 1). The failure of the disease to appear in a given generation has been explained on the assumption that the condition may be transmitted in a latent or unrecognized form, or that the well phenotype may be the carrier of the tendency.[1] It seems highly probable that the failure of the process to be recognized in those families which have noted a disappearance of the disease in the line of inheritance for one generation (or more) may

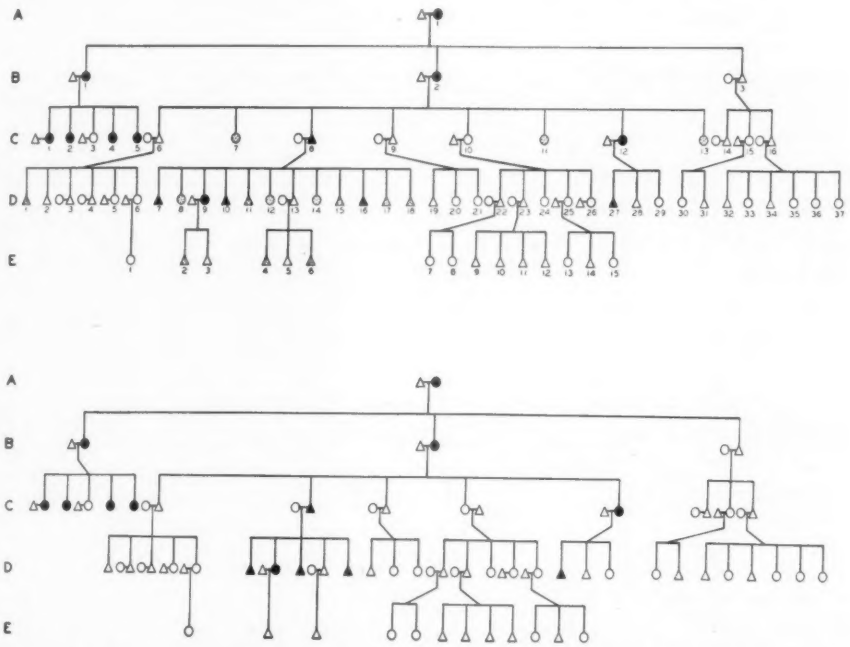


CHART 1.—Showing, graphically, the descendants of Mrs. X, who had multiple skin tumors and a "lump as large as a bucket hanging from her neck."

Mrs. X, who is the only known member of the oldest generation, is represented as A1. The affected individuals are shown in solid black circles (females) or triangles (males). The stippled figures represent those children who died in infancy, and it is uncertain whether or not they would have shown stigmata of von Recklinghausen's disease. The members of the youngest, or E, generation are too young as yet to be sure they are all unaffected.

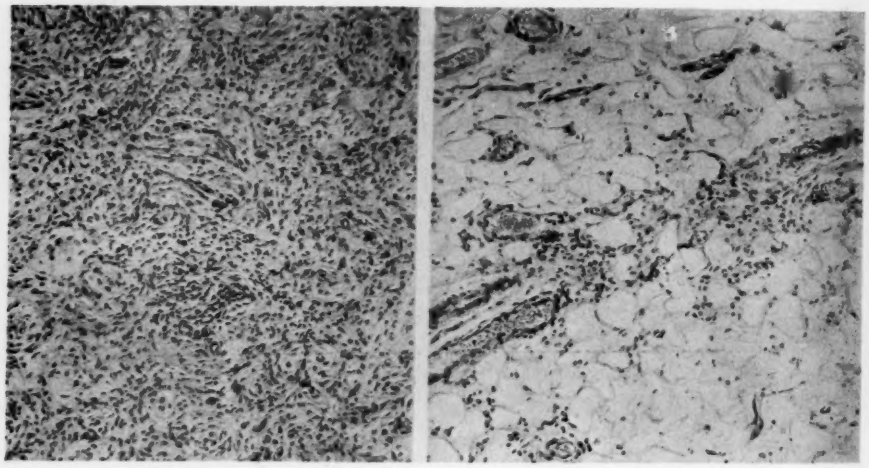
The lower chart represents the same family tree, omitting those children dying early in life, better to show the mendelian inheritance of the disease.

be due to its existence in the members of that apparently unaffected generation in a mild form, the so-called *forme fruste* which is characterized only by a number of *café au lait* spots.

The Pathologic Aspects of Multiple Neurofibromatosis.—Although the association of the multiple encapsulated subcutaneous tumors with the nerve trunks was recognized in 1849[11] (33 years before von Recklinghausen's description of the condition), there have been numerous divergent interpretations of the morphology of the disease since that date.*

* It is of interest to record here that a similar condition has been described in animals by veterinarians.[12]

Neurofibromata may be found on the branches of the cutaneous nerves, along the trunks of the nerves of the thorax and extremities, and arising from the cords and trunks of the brachial and lumbar plexus. They may also arise from the paravertebral sympathetic chain, the visceral sympathetic plexus or the nerve supply of the intestinal tract, and enlargement of the periarterial sympathetics suggesting such a tumor formation has been recorded.[13] Also, tumors are at times found on the cranial nerves within and without the cranial cavity and along the spinal nerves before they emerge from the spinal canal. Growths arising from the meninges,[14] intracerebral astrocytomata and ependymomata and syringomyelitic changes[15] in the spinal cord have been reported in certain cases of von Recklinghausen's disease.



A B

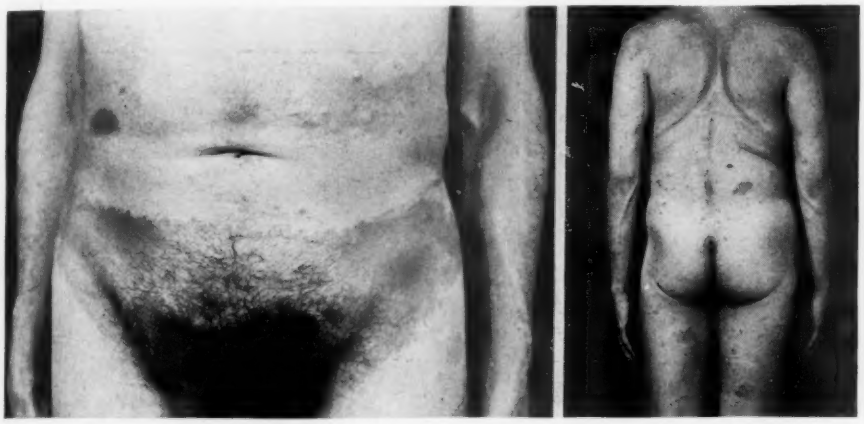
FIG. 1.—(A) The disorderly cellular arrangement seen in the microscopic section of the tumors of von Recklinghausen's disease (Fig. 12) is well represented by the area shown above. In certain tumors, the fibroblastic element predominates to such a degree that the palisading of the nuclei and regularity of the cells suggests the picture seen in a neurinoma. Other nodules from the same patient, having a predominance of loose areola stroma, may show the appearance of the tissue removed from the pachydermatocele (B).

(B) Section of the jelly-like material from the patient shown in Figures 15, 16 and 17, with its thin-walled, large blood vessels and acellular structure, contrasts sharply with the fibroblastic reaction in other lesions of the same disease process. The variations in, or predominance of, one of these contrasting types of tissue accounts for the wide differences in the physical characteristics of the individual tumors.

At the present time, among those[16] who have investigated the structure and origin of the multiple neurofibromata, there is some difference of opinion concerning the exact interpretation of their observations. Verocay and Masson[17a] believe that the tumors are neuroectodermal in origin, arising from the sheath of Schwann, and Cushing[17] has recently called attention to early experimental work showing that neuroectoderm, although peculiar in its origin, should be considered a sheet of cells such as the mesoderm which possesses the ability under certain circumstances to give rise to a variety of tissues. None the less, Penfield's[18] belief that the multiple neurofibromata of von Recklinghausen's disease are of mesodermal origin, arising from the epineurium, perineurium and endonerium of the nerve bundles, has gained wide attention at present.

The latter author describes a characteristic section of one of these nerve tumors as showing "tangled reticular areas where the nuclei are not arranged in any particular order (Fig. 1 A) and where there is an obvious confusion of connective tissue. Nerve fibers may be demonstrated in the capsule and passing through the tumor itself and collagen stains of the reticular areas show a crossing and intermixture of fine collagen fibers. In areas of degeneration or softening, much hyaline material may be present, and while the nerve fibers passing through the tumor are usually nonmyelinated, myelinated fibers may be present. Areas of perineural fibroblastic reaction may be so extensive as to almost replace the more reticulated tissue."

The skin pigmentation, which is seen on all affected individuals, may be



A B

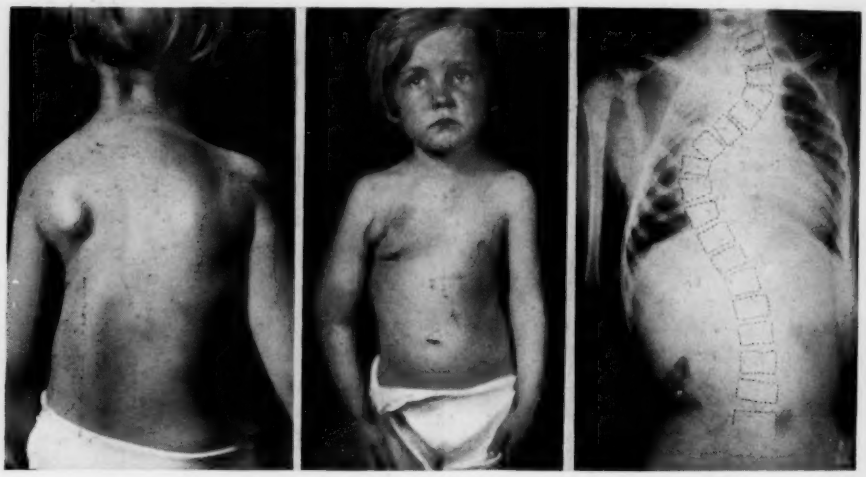
FIG. 2.—(A) A symmetrical, triangular pigmented area having all the characteristics of a large *café au lait* spot may be seen covering the lower abdomen, inguinal regions, and extending down onto the genitalia of a 23-year old student. More characteristic, is the elliptical *café au lait* spot visible on the right side of the abdominal wall, lateral to and just above the umbilicus. The small pigmented dots are freckles. Also, a number of small subcutaneous tumors may be seen.
(B) On the lower back and thighs are medium sized *café au lait* spots. The scoliosis occurring so frequently in individuals affected with von Recklinghausen's disease may be seen in the posterior view.

represented by a moderate freckling in mild cases, while in others it may be diffuse and frequently has a symmetrical distribution (Fig. 2). True nevi, although not characteristically associated with the disease, are at times seen and may reach the size of the so-called "bathing trunk nevi."[19] The texture of the skin of a *café au lait* spot may be coarser than normal but usually there is no appreciable gross change aside from the increased pigmentation.

It is stated that microscopic sections of the *café au lait* spots may show an increase in the pigment of the basal layer of the epithelium.[20] This has not been noted in the group of cases seen by us, but these have shown an increase in the number of melanophores in the deeper layers of the dermis, especially about the small blood vessels, a change which may well account for the pigmentation.

The skeletal changes associated with multiple neurofibromatosis have been well described by Brooks and Lehman.[21] Scoliosis (Fig. 3) and irregularity

in the shafts and differences in the length of the long bones have been the abnormalities most frequently noted. Pseudarthroses and abnormal curvatures of the bones have also been reported.[20] The bone changes have been interpreted by Brooks and Lehman as due to the involvement of the bone by the growth of tumor tissue characteristic of von Reckinghausen's disease. They state that the growth of a neurofibroma of a periosteal nerve may be accompanied by a certain amount of bone destruction and bone regeneration. If in the process of development the osteogenetic element of the periosteum covers the tumor, a thin shell of bone may be formed, giving the appearance of a subperiosteal bone cyst. If the growth destroys the epiphyseal cartilage, shortening may follow, while with the lesion limited to the shaft, lengthening



A B C

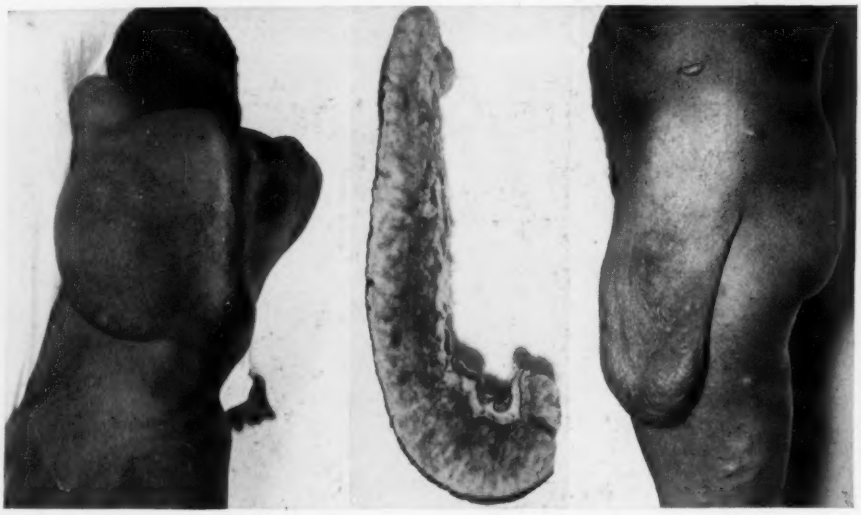
FIG. 3.—Hosp. No. 38744: D. H., female, white, age four, had several areas of skin pigmentation present at birth, and the spot above the right scapula has grown progressively larger since. The curvature of the spine was first noted by the parents when she was three years of age, and this too had increased during the year preceding admission to the hospital. On entry into the hospital, she showed multiple neurofibromatosis with numerous subcutaneous nodules and *café au lait* spots (A and B). The scoliosis so frequently encountered in patients having von Recklinghausen's disease is shown in a marked degree (A, B, and C).

may occur. Scoliosis may follow abnormal softening of the vertebrae as a result of the tumor growth, or it may be secondary to growth disturbances in the lower extremities.

In general, neurofibromata are benign encapsulated tumors, although at times their capsules may be poorly defined. They do not, as a rule, destroy the nerves from which they grow. Malignant tumors occur in from 12 to 14 per cent of patients showing stigmata of von Recklinghausen's disease. These are usually fibrosarcomata, but epithelial neoplasms, thought to arise from the sheath of Schwann, have been reported.[22] All grades of malignancy may be encountered in a large series of these lesions, and, although local invasion is the usual method of extension, metastases to distant organs, particularly the lungs, may occur. Rarely, metastases may occur to adjacent lymph nodes

(Fig. 14). Not infrequently, more than one malignant tumor may arise at different levels along the same nerve trunk.

The Clinical Features of Multiple Neurofibromatosis.—It has well been said that multiple neurofibromatosis is a disease of protean manifestations,[23] for the individual variations in the classic clinical pictures alone are without limit. Although the stigmata of the process, either subcutaneous tumors or areas of skin pigmentation, have not infrequently been observed in infants, the presence of the disease has been more often recognized at puberty as it is more usual at this period for the subcutaneous nodules to make their first ap-



A B C

FIG. 4.—Two patients illustrating the difference in appearance of fibroma molluscum (A and B) and plexiform neuroma (C). (A) Fibroma Molluscum. This pendulous tumor composed of fibrous tissue (B) overlay the back and dorsal vertebrae of a colored man, age 25, who was hospitalized because of a paraplegia of two weeks' duration. At operation, the spinal cord was found to be pulled completely apart by traction over the gibbous. There was no evidence that pressure had been made on the cord at the point of division.

(B) A gross section of the fibroma molluscum shown in (A) reveals an unusual amount of pigmentation. On microscopic examination, this tumor was composed of uniform fibrous-like tissue with large collections of melanin scattered throughout the deeper portion of the growth.

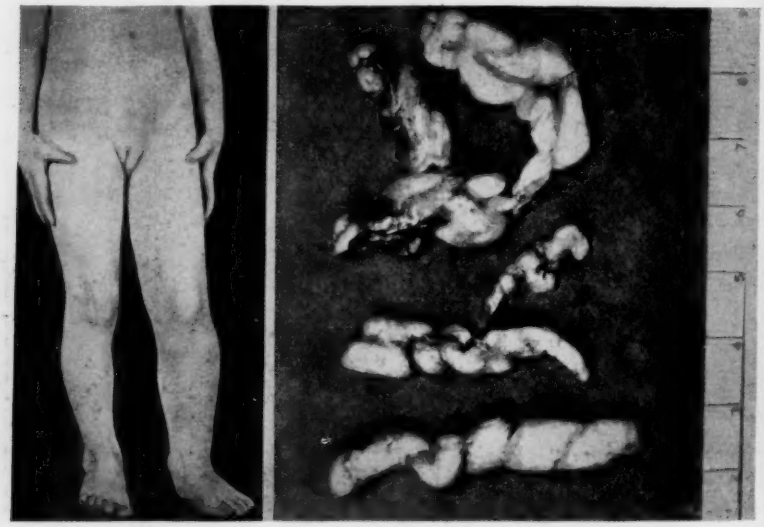
(C) The growth present over the left hip of another patient is irregular rather than uniform in consistency, and on palpation gives the impression of being composed of interlacing nodular cords and is more likely a plexiform neuroma. This 39-year old colored woman first noticed a "fleshy lump" here when she was age 12, and the tumor has increased progressively in size since then. There is also a hard, tender, painful mass on the medial aspect of the left upper thigh which has grown rapidly during the past three months and is clinically a sarcoma.

pearance or to reach such a size that they are noticed by the patient or his family.

The usual clinical picture is that of multiple sessile or pedunculated soft or elastic tumors (which may number as many as 4,500)[4] associated with *café au lait* spots (Fig. 3), both the tumors and pigmented areas showing infinite variations as to size, number, consistency and location. In addition to the characteristic well-defined, more or less globular subcutaneous nodules over which at times the skin may be atrophic, one may encounter the soft pendulous masses of fibroma molluscum (Fig. 4 A and B), or the worm-like plexiform

neuromata (Fig. 4 C), which have acquired special designation as clinical and pathologic variants of the lesions usually seen in von Recklinghausen's disease. Elephantiasis neuromatosa, an enlargement of an extremity resembling that seen in elephantiasis (Fig. 5), is an infrequent variant of the classic clinical picture, and is associated with tumor formation or diffuse enlargement of many of the nerves of the limb, at times even the sympathetics being involved.[13]

The *café au lait* spots, varying in size from freckles to pigmented areas 10 cm. or more in diameter, are found in all cases, and although they are usually ellipsoid in shape they may be irregular in outline. They are often symmetrically distributed over the trunk and extremities (Fig. 3). Nevus anemicus has been described[24] in association with the disease, and while nevi



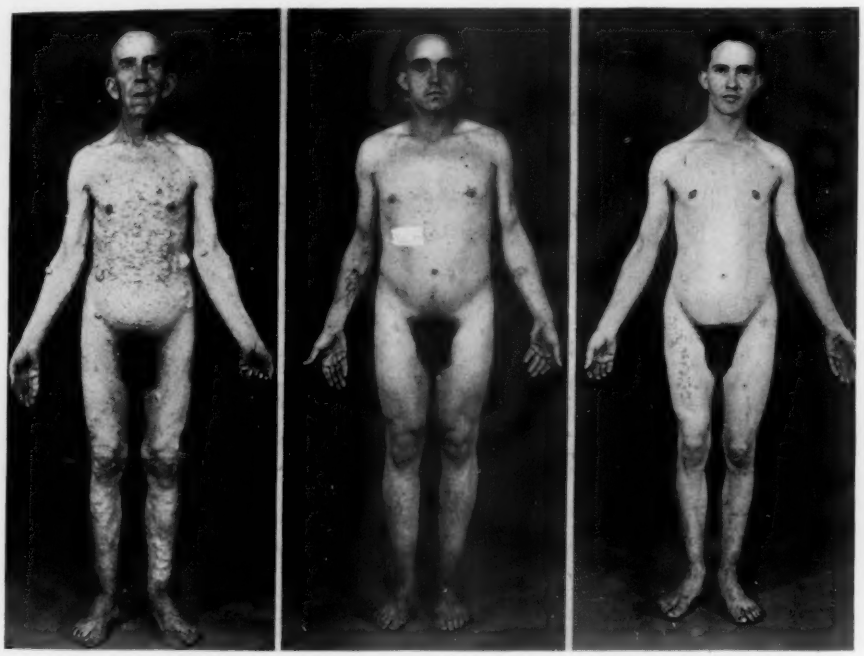
A B

FIG. 5.—Elephantiasis Nervorum (Lewis, Dean, and Hart, Deryl.: Tumors of Peripheral Nerves. ANNALS OF SURGERY, 92, 961–983, 1930).
The left lower extremity is enlarged. Multiple nodules can be palpated along the nerves, especially over the short saphenous. A biopsy was performed and the nerves were found to be irregularly enlarged throughout their entire exposed length, varying in size from one to several millimeters in diameter.

and angiomata are not infrequently present these do not bear the same intimate relationship to the multiple neurofibromata as do the *café au lait* spots, and should not be confused with the latter.

Sharpe and Young[3b] have emphasized recently, that one of the most outstanding features of von Recklinghausen's disease is its progressive course. As the individual matures the tumors increase in number and size, and the skin pigmentation becomes more widely distributed. This course of events was brought forcibly to our attention by one of our patients who stated that as a boy he had few tumors, but, that with the advancing years, not only did the original tumors enlarge, but new ones appeared so that his trunk became studded with them (Fig. 6). One of his sons, as a child, had only a few *café au lait* spots, noticed the appearance of subcutaneous tumors at puberty, and, as he has grown older, both types of lesions have increased in size and number.

Unrelated or intercurrent pathologic disturbances and even normal physiologic changes may exert a definite influence on the evolution of the disease process. It is well known that puberty has a stimulating effect on the development of the lesions and pregnancy as a rule is attended by an increase in the size and number of tumors and *café au lait* spots. We have observed an increase in the intensity of the skin pigmentation of one of our patients during pregnancy. Recession of both types of lesions following delivery, and exacerbations during subsequent pregnancies have been reported.[25a,b,c] Intercurrent



A B C

FIG. 6.—(A) E. P., who is at present 62 years of age, is represented by the triangle C 8 in Figure 1. As a young man, he had few subcutaneous tumors, but these became larger and many others appeared as he grew older.

(B) R. N. P., his oldest living son (D 10 Fig. 1), as a child, had a few *café au lait* spots, but developed subcutaneous tumors at puberty, and, as he has grown older, both types of lesions have increased in size and number. A tumor removed from the abdominal wall showed the microscopic appearance of a neurofibroma of von Recklinghausen's disease.

(C) J. R. P., another son of E. P. (D 13 Fig. 1), has no demonstrable neurofibromata or *café au lait* spots.

infections may also cause an increase in the symptoms and signs of the condition and these may recede following recovery.

A high incidence of feeblemindedness has been recorded in those showing marked involvement[4] and we have noted a certain lack of mental acuity in the more markedly affected members of the family reported by us (Chart 1). The lack of fertility in some families showing extensive neurofibromatosis has been ascribed to sexual impotence and the dying out of other strains has resulted from a high infant mortality (Chart 1). Obvious endocrine dysfunction has been observed in many instances.[23, 26] The pigmentation in certain patients

has been explained by disordered adrenal function, and acromegalic features in others have been related to pituitary dysfunction. However, there is little evidence pointing toward a constant disturbance of function of any of the endocrine glands as the underlying cause of multiple neurofibromatosis and manifestions of such dysfunction in a particular individual may be attributed to pressure effects of neurofibromata on the gland in question, or to some coexistent developmental disturbance.

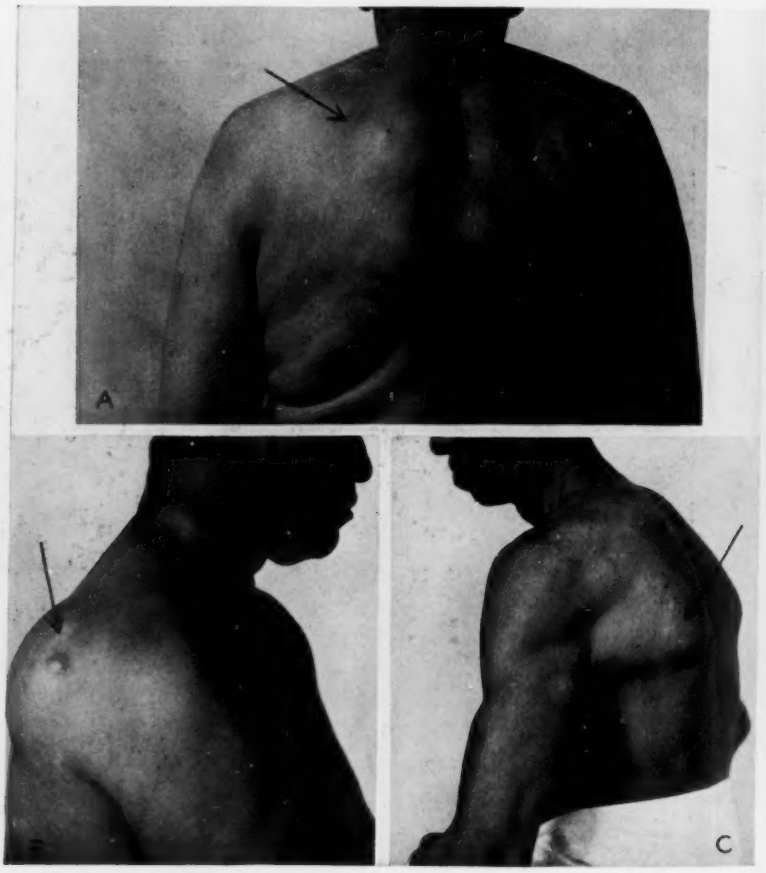


FIG. 7.—Lipomata in the subcutaneous tissue overlying the scapulae of a mother and two sons. These are the only lipomata present in these patients. Two of the patients show sebaceous cysts which might increase the possibility of confusing this condition with neurofibromatosis.

Although the clinical and pathologic variations discussed above go far toward making multiple neurofibromatosis a disease of protean manifestations, none the less, it is frequently the complexity of the symptoms and signs resulting from one of the complications of the malady which presents a major problem in clinical interpretation. Both the bizarre forms of the disease and the complications present problems in differential diagnosis.

Differential Diagnosis.—It has been necessary, in our experience, to dif-

ferentiate multiple lipomata (Figs. 7 and 8), multiple xanthomata, multiple epidermoid cysts (to be published), lymphosarcoma and Hodgkins' disease from multiple neurofibromata. Leprosy, especially in subtropical countries, must also be considered in patients with numerous subcutaneous tumors. Although the absence of *café au lait* spots is usually sufficient to eliminate von Recklinghausen's disease as a probability in a patient showing symptoms and signs suggestive of one of the diseases noted above, the clinical differentiation is made difficult in many individuals by the presence of a certain amount of normal freckling. Scoliosis associated with multiple subcutaneous nodules is also of value as a diagnostic sign, although scoliosis due to other causes is

A B C

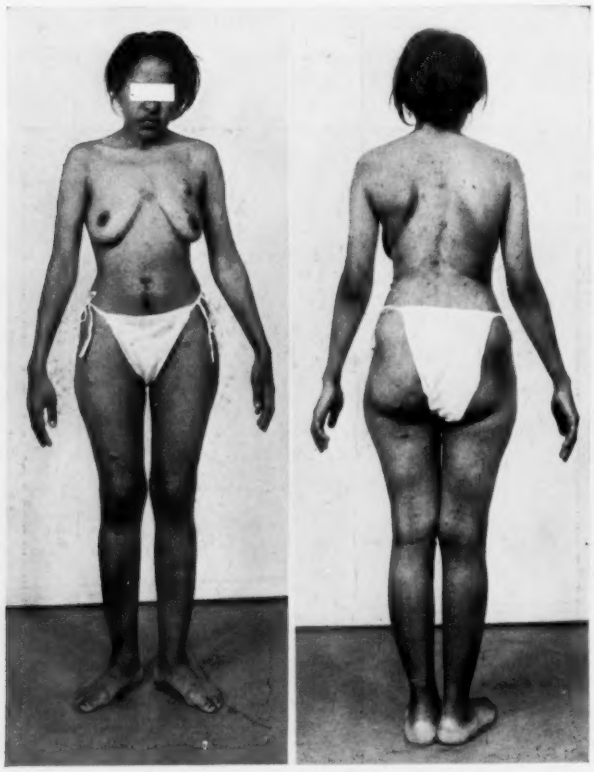
FIG. 8.—The colored man, age 36, shown above (A and B), first noticed a small mass on his right buttock as a child, and the tumor had grown progressively larger until the time of his entry into the hospital. Although he had been able to walk about the greater part of his life he had been completely bedridden during the two years prior to admission. The growth was thought to be a fibrolipoma until the skin pigmentation and multiple subcutaneous nodules on the extremities and trunk were discovered. Microscopic examination of one of the small tumors, which was removed, showed the characteristic appearance of a neurofibroma of von Recklinghausen's disease. Microscopic sections of tissue taken from the large growth showed very compact fibrous tissue but nothing suggestive of a malignant tumor. However, this would not rule out a malignant change in other parts of the growth.

The patient's family history could not be followed for more than two generations. His mother, shown above (C), had multiple neurofibromatosis.

common and its presence together with subcutaneous tumors cannot be relied upon as an absolute criterion for the diagnosis of multiple neurofibromatosis. In the usual case, the character and distribution of the subcutaneous tumors and *café au lait* spots make the clinical diagnosis an easy one. When there is any doubt as to the diagnosis, pathologic study of the lesion in question is indicated, especially should the clinical features of one or several of the tumors raise the question of malignancy.

The Surgical Problems Presented by Multiple Neurofibromatosis.—The

patients who develop surgical complications as a result of von Recklinghausen's disease may be classified in three main groups. The largest group consists of individuals having neurofibromata in such a location that pressure from the tumor growth affects the function of one or more important organs or structures. In the second group are the patients who develop a malignant growth in the course of the disease; and the third is made up of those patients



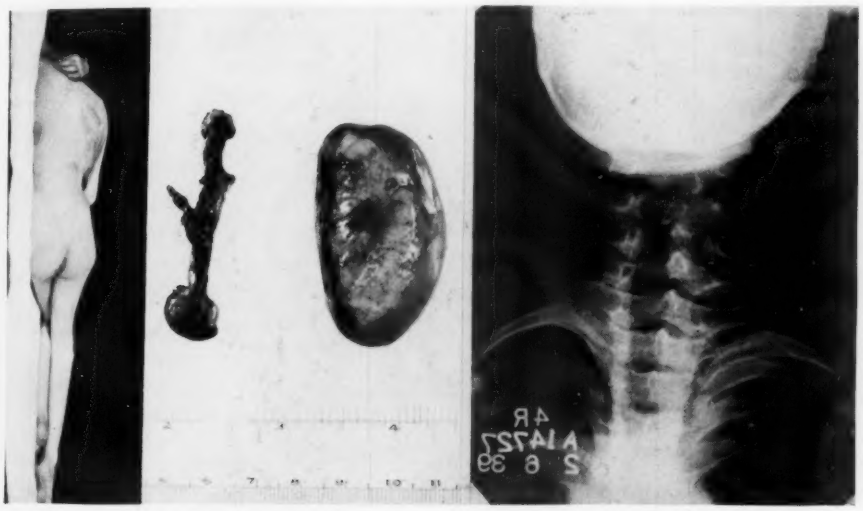
A B

FIG. 9.—This 26-year old woman was admitted to the Tumor Clinic of the Duke Hospital, complaining of a painful tender tumor in the left breast above the nipple. She had noticed the presence of painless subcutaneous tumors since early childhood, all of which increased slowly in size as she grew older. The growth of which she complained had been present for five years but had been painless until three months before her visit to the hospital when it became tender and caused a drawing pain in the adjacent area. Following excision of the pigmented, conical mass, which on removal was found to be somewhat nodular, she has been entirely free of pain for over a year. Microscopic study of the tissue showed a neurofibroma such as is encountered in von Recklinghausen's disease, with nothing to suggest a malignant growth. Note also the scoliosis.

having a hemorrhage into a large pachydermatocele, which is occasionally seen in neurofibromatosis.

The pain caused by the growth of a tumor on a peripheral nerve has previously been reported,[27] and a case recently seen by us illustrates this pressure effect (Fig. 9). The bizarre symptoms and signs resulting from intracranial tumors associated with generalized neurofibromatosis, have been

commented upon by Cushing[17] and others.[5, 14] Cranial nerve palsies and clinical signs of pressure of the tumors on the brain stem are not uncommon. Tumors arising from the nerve roots within the spinal canal are occasionally seen and may result in signs of cord compression (Fig. 10). Partial obstruction of the pharynx from neurofibromata,[28] macroglossia from similar lesions in the tongue[29] and tumors in the neck arising from the cervical nerves and brachial plexus may occur (Fig. 16). We have studied one patient, an individual with numerous masses in the neck and an incomplete tracheal obstruction produced by mediastinal neurofibromata, whom we wish to report in



A B C

FIG. 10.—(A) This patient, a white boy, 16 years of age, was admitted to the Neurosurgical Service of the Duke Hospital for treatment of a paraplegia of six years' duration. Since birth, he had had a boggy, subcutaneous tumor over the right scapula and, during the past year, other subcutaneous tumors and *café au lait* spots had appeared. The paralysis developed gradually over a period of "several months" and the loss of motor function was followed shortly by anesthesia over his lower extremities and trunk up to the level of the nipples. A laminectomy revealed an intraspinal neurofibroma (B) originating from the eighth cervical nerve root, extending from the sixth cervical to the second thoracic vertebrae, completely filling the spinal canal, extending out into the foramina and, undoubtedly, connected to the tumor in the chest (C), which had reduced the cord to a thin filament. On an adjacent nerve root there were two small neurofibromata which were also removed with the nerve root.

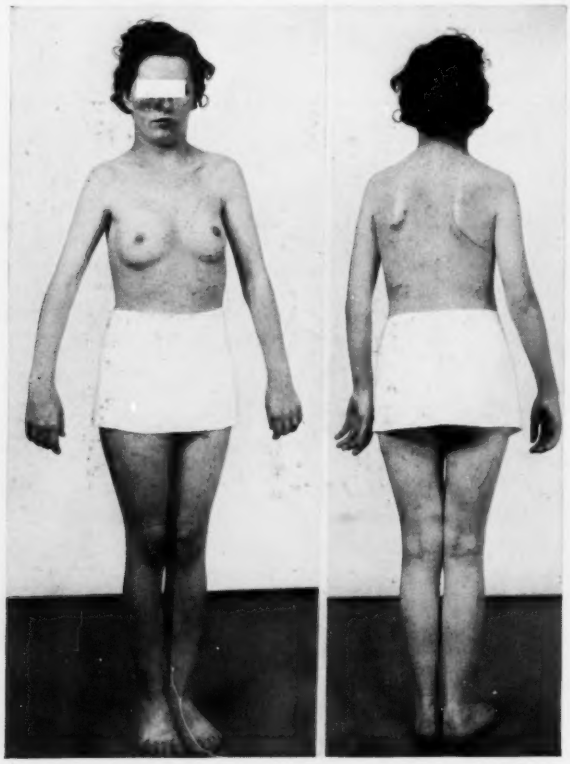
(C) Roentgenograms of the chest, taken before operation, showed a tumor in the upper left chest and lower neck, and a diagnosis of an hour-glass tumor was made. The intrathoracic tumor has not been removed since it is producing no symptoms and it seems unlikely that there will be any return of function in the cord.

detail, since she illustrates so well one of the surgical problems resulting from pressure symptoms.

Case Report.—Hist. No. A-6790: V. E. R. (Fig. 11), white, female, age 19, was referred for treatment because of a mass in the upper mediastinum which was partially compressing the trachea and the upper lobe of the right lung. There was no history of skin pigmentation or of subcutaneous tumors occurring in other members of the family. At age 9, she had an attack of Rocky Mountain spotted fever and following this a small mass was noted in the subcutaneous tissue over the left shoulder. Four years before admission, at age 15, she developed intermittent attacks of dull aching pain in the region of the right shoulder, right clavicle and right side of the chest, which had persisted. The

episodes of pain came on at intervals of several months and were of three to four days' duration. For three weeks before she entered the hospital, she had experienced some difficulty in breathing. Nodular masses were noted on both sides of her neck two weeks before entry and had increased gradually in size.

Physical Examination revealed several *café au lait* spots on her trunk and numerous small, soft and elastic tumors in the subcutaneous tissues over her back and extremities. On the right side of the neck, anterior to and beneath the sternocleidomastoid muscle, were several firm, slightly tender masses which resembled a chain of enlarged cervical



A B

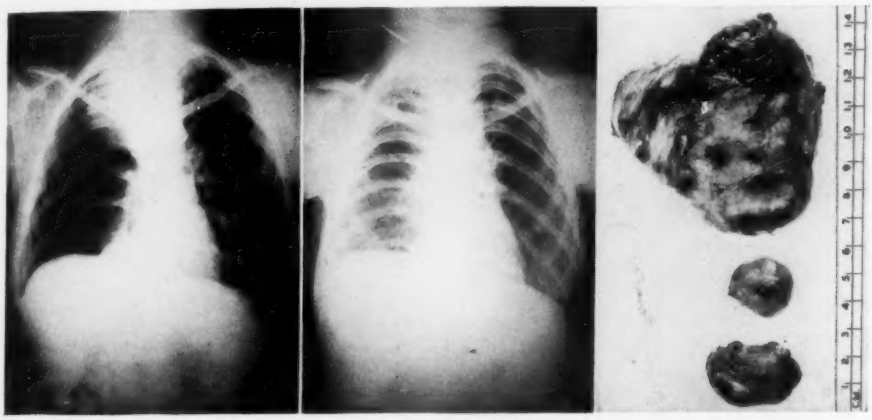
FIG. 11.—This white girl, age 19, was referred to the Duke Hospital for treatment of a growth in the upper mediastinum partially compressing the trachea and the upper lobe of the right lung and causing pain in the right chest and shoulder. When first seen, in another hospital, the clinical impression was either Hodgkin's disease or lymphosarcoma, since she had numerous masses in the neck and both axillae, resembling enlarged lymph nodes. A biopsy of one of the tumors showed the characteristic picture of a neurofibroma of von Recklinghausen's disease and further examination revealed numerous subcutaneous tumors and *café au lait* spots. The scar from the thoracotomy can be seen located medially and inferiorly to the scapula. The moderate scoliosis is not seen clearly in (B).

lymph nodes. Several tumors in the axillae felt much like enlarged lymph nodes but two removed for study before admission had proved to be neurofibromata. There was a scoliosis of the dorsal spine with the convexity to the left.

The laboratory studies of the blood and urine revealed normal findings and the blood Wassermann was negative. A roentgenogram of the chest (Fig. 12 A) showed a rounded mass present in the upper mediastinum which extended outward to compress the upper lobe of the right lung.

Our impression was in agreement with the previously made diagnosis of von Recklinghausen's disease with intrathoracic and probably mediastinal neurofibromata. In view of the patient's respiratory symptoms it was thought advisable to attempt removal of the intrathoracic tumors.

Operation.—August 30, 1938, Dr. Deryl Hart: Under nitrous oxide and oxygen anesthesia, a posterior thoracotomy was performed on the right side. The incision exposed, in the subcutaneous tissue and muscle, a large number of small, elongated neurofibromata. Three firm tumors (Fig. 12 C) located in the costovertebral sulcus, one of which extended into the mediastinum partially compressing the trachea, were exposed and removed, relieving the patient of all respiratory difficulty. Pathologic examination of the tumors showed them to be neurofibromata, similar in appearance to those encountered in von Recklinghausen's disease (Fig. 1 A). A roentgenogram of the chest



A B C

FIG. 12.—Roentgenograms of the chest of the 19-year old girl shown in Figure 11, taken before (A) and after (B), a posterior thoracotomy with removal of the intrathoracic neurofibromata. The rounded mass in the upper chest, extending into the mediastinum and partially compressing the trachea and the upper lobe of the right lung, seen in (A), was found at operation to be composed of three tumors (C) (for microscopic appearance see Figure 1A) which apparently arose from the paravertebral sympathetic chain, although the possibility of their origin from the intercostal nerves at the vertebral foramina (hour-glass tumors of Heuer and others) could not be completely excluded. Following their removal the upper lobe of the right lung reexpanded (B) and all pain and symptoms of tracheal obstruction disappeared. Since operation, the right hand has remained persistently warmer than the left, probably as a result of damage to the sympathetic nerve supply.

subsequent to operation showed re-expansion of the right upper lobe and some general fibrosis of the right lung (Fig. 12 B).

It seems most likely that these tumors originated from the thoracic sympathetic trunk since they were most firmly attached in this region and the right hand and arm have been warmer than the left since operation. They may have originated from the thoracic nerves at their point of emergence from the spinal canal but there was no evidence of any intraspinal extension as in the hour-glass type of tumor described by Heuer, Andrus and Taylor.[30] Hypesthesia has been present over the right chest since operation but this is limited to the area innervated by the nerves that were divided in making the thoracotomy incision.

The case reported above also showed the dorsal scoliosis (Fig. 10) so frequently encountered in this disease, in this instance probably the result of the intrathoracic tumors. The change in the spinal column may be marked and,

instead of scoliosis, a gibbous may develop and may be followed eventually by a paraplegia. This course of events, previously reported,[31] was seen in a patient recently studied in the Duke Hospital, in whom a laminectomy disclosed the spinal cord to be completely torn across by traction over the kyphos (Fig. 13).

Tumors of the abdominal viscera have been noted frequently but apparently they rarely give rise to pressure symptoms. An exception to this was the case of a patient[32] with an abdominal neurofibroma, causing marked abdominal distension and dyspnea, which was thought to have arisen from the sympathetic nerves of the ovary. Tumors of the retroperitoneal nerves are more common

A B

FIG. 13.—This colored man, age 25, was found at operation to have the spinal cord completely divided by traction over the extremely pronounced kyphos. (See Fig. 4 A and B, same patient). He suddenly developed a paraplegia two weeks before admission to the hospital. In addition to the pendulous fibroma molluscum below the gibbous, he also showed numerous neurofibromata in the subcutaneous tissues of the trunk and extremities.

and have been reported as a cause of dystocia during pregnancy,[25c] while neurofibromatosis of the prostate and bladder may be a cause of serious urethral and ureteral obstruction which may result in uremia.[33]

Large benign neurofibromata may cause some discomfort from their size. However, a rapidly growing tumor should make one suspicious of malignancy. The incidence of sarcomatous degeneration in von Recklinghausen's disease has been found to vary from 12 to 13 per cent.[34a, b, c] Stewart and Copeland,[35] reporting 21 cases of neurogenic sarcoma developing in patients with multiple neurofibromatosis, found two peaks in the curve of age incidence—one between the ages of one and ten years and the other between 30 and 50 years. Metastases have been noted in 22 per cent of such cases.[34c] Once malignancy develops, the prognosis is poor, and of the group of patients reported by Stewart and Copeland[35] none was well at the end of five years. Local recurrence, which usually follows excision of one or more malignant tumors

arising from the same nerve sheath, often necessitates secondary operations. The majority of the patients finally die as a result of local recurrences or metastases. Metastasis to regional lymph nodes, an infrequent occurrence, is illustrated by one of our recent cases (Fig. 14). Radical surgical excision or amputation has been the usual treatment of these sarcomata and remains the accepted procedure. Stewart and Copeland[35] state that certain tumors of long duration have recurred after operation and the patient has been made worse by excision. They also suggest that a policy of nonintervention may be the treatment of choice for slow-growing malignant tumors of this type. Irradiation therapy of these sarcomata has not been standardized and while it may be beneficial in some cases no conclusions can be drawn as to its effectiveness in general.

FIG. 14.—Metastases in the inguinal lymph nodes, 15 months after amputation for a spindle cell sarcoma arising in the upper end of the right tibia in a patient with von Recklinghausen's disease. This patient, a white man, age 35, had multiple neurofibromata with characteristic *café au lait* spots. Sections of the growth in the tibia showed a cellular structure similar to other sarcomata developing in our group of patients with von Recklinghausen's disease. A roentgenogram of the chest, taken before amputation, showed, on the left, a tumor, projecting above the diaphragm, near the heart, and thought to be a neurofibroma and not a metastasis. Since amputation, this has increased somewhat in size, is not located within the lung, and is not considered to be a metastasis.

The second case we wish to report in detail, presents an excellent example of the third type of surgical complication seen in von Recklinghausen's disease. This patient eventually died of asphyxia caused by a rapidly growing and clinically malignant tumor in the neck, but entered the hospital on account of symptoms resulting from a spontaneous hemorrhage into a pachydermatocele over the lumbar region.

Case Report.—Hist. No. 69788: M. E. S. (Figs. 15, 16 and 17), white, female, married, age 23, was admitted to the Duke Hospital, July 12, 1936, complaining of a swelling over the lower back of nine days' duration. Her mother and one sister had skin tumors over the trunk and extremities similar in character to those present on the patient. As a child she had a club foot on the right side which had been partially corrected by operations when she was 17 and 19 years of age. Not until she was 13 years of age were the subcutaneous nodules noted over the trunk, and at the age of 17, a mass in the left side of the lower neck first appeared (Fig. 16). This increased very gradually in size until the year before admission, when its growth became accelerated.

The illness for which she sought hospital care developed nine days before entry, when a "lump of muscle," which she had "always had" over the lumbar region, enlarged rapidly during a period of 48 hours. At this time, she became very weak and fainted when she attempted to get out of bed. There was no history of any injury, and aside from the aching discomfort in the region of the tumor she was free from pain. The family physician aspirated blood from the swelling and regarded the condition as a subcutaneous

hemorrhage. Cold packs were applied to this area which became somewhat softer, but since it did not decrease in size she was eventually sent to the hospital, nine days after the onset of her acute symptoms.

FIG. 15.—Same patient as shown in Figures 16 and 17. This patient, white, female, age 23, was admitted to the Duke Hospital nine days after a spontaneous hemorrhage into the pachydermatocele over the lumbar region. From a small, inconspicuous "lump of muscle" the tumor grew to the size of a "football" within a few hours. The subcutaneous nodules and *café au lait* spots over the trunk and extremities have been present since adolescence. On the side of the ankle can be seen the scar resulting from operations for a congenital club foot.

FIG. 16.—Same patient as shown in Figures 15 and 17. The rapidly growing tumor present on the left side of this patient's neck was clinically malignant, and eventually caused her death from asphyxia. At the time of operation for a hemorrhage into the pachydermatocele, respiratory embarrassment due to this growth necessitated intratracheal anesthesia. She would allow no treatment for this mass and it caused her death by asphyxia five months later.

Physical Examination showed a pale, well nourished patient, with normal temperature, pulse and respiration. The skin was studded with multiple, soft, elastic tumors, characteristic of those seen in von Recklinghausen's disease, and there were numerous

café au lait spots scattered over the trunk. A certain amount of mental retardation was obvious. On the left side of the neck, beneath the carotid, and extending down behind the clavicle and sternum, displacing the trachea to the right, was a firm, fixed tumor, approximately 12 cm. in diameter (Fig. 16). Examination of the heart, lungs and abdomen was essentially negative. Overlying the lower lumbar region was a mass about the size of a football, over which the skin was tense, shiny, and discolored by the underlying hematoma. The swelling was warm, pseudofluctuant and nontender (Fig. 17). The right leg was larger than the left and the right foot, in addition to being fixed in dorsiflexion at the ankle, showed, on the anterolateral aspect, scars of the previous operations.

FIG. 17.—Same patient as shown in Figures 15 and 16. The blue discoloration of the skin overlying the hemorrhage in the pachydermatocele resulted in the diagnosis of subcutaneous hemorrhage by the patient's family physician. At operation, more than a liter of partially clotted blood was evacuated from the hematoma in the gelatinous tumor tissue, and the greater portion of the tumor was excised (see Figure 1 B for microscopic appearance). The patient made a satisfactory convalescence and she had no further bleeding during the remaining five months of her life (Fig. 16).

Studies of the blood revealed: Hb. 44.2 per cent, RBC, 3,700,000; WBC 9,400. The urine and blood Wassermann examinations were negative. The blood cholesterol was 183 mg. per cent. Roentgenograms of the lumbar spine showed an enormous soft tissue tumor in this region and an erosion of the spinous processes of the upper three lumbar vertebrae.

A diagnosis of hemorrhage into a pachydermatocele over the lumbar region was made and after transfusions (totaling 1,500 cc.), which resulted in raising her hemoglobin to 81 per cent, the hematoma was evacuated under nitrous oxide and oxygen anesthesia. Since respiration was considerably embarrassed by the cervical tumor it was necessary to use intratracheal anesthesia. The liquefied blood and blood clot were removed from the surrounding gelatinous tissue which represented the preexisting tumor. There was a little oozing from smaller vessels in the walls of the resulting cavity after evacuation of the hematoma but no large bleeding point could be seen. The gelatinous tumor tissue was removed as widely as possible, exposing the lumbar fascia in the depth of the wound. After closure of the skin a pressure dressing was applied to obliterate the dead space. Six weeks later there was only a small swelling in the lumbar region occupying the site of the former pachydermatocele.

She refused treatment for the rapidly growing cervical tumor and her family physician wrote, five months later, that she had died rather suddenly of asphyxia as a result of this

growth which had continued to increase in size after her return home. There was no recurrence of hemorrhage into the tumor over her lumbar region.

We have been able to collect from the literature seven other cases of hemorrhage into large tumors observed in patients having multiple neurofibromata, which are briefly summarized below:

ABBREVIATED CASE REPORTS OF SEVEN INSTANCES OF HEMORRHAGE INTO NEUROFIBROMATA

(*From the Literature*)

Case 1.—Reported by Heuer,[19] 1917:

A 24-year old machinist was first operated upon in 1906 for hemorrhage into a large nevus over the lumbar region, following slight trauma. Spontaneous hemorrhages into the pachydermatocele necessitated reoperation in 1907, 1911 and 1912. A spina bifida occulta and meningocele were present beneath the tumor.

Case 2.—Reported by Carrington and Bullitt,[36] 1926:

A 22-year old Negro laborer developed a hemorrhage into a tumor in the right flank. The tumor, originally as large as an orange, became, in the course of two hours, larger than the patient's head. Evacuation of the hematoma, six days later, was followed by healing.

Cases 3, 4, and 5.—Reported by Heuer and Bell[37] 1931:

Case 3.—A 40-year old white man, as the result of a fall, developed a hematoma in a pachydermatocele on the left buttock. Spontaneous evacuation of the blood clot occurred, but the wound became infected and did not heal completely. When the acute infection subsided the tumor was excised but the patient died about three years later from a malignant growth arising from the right sciatic nerve.

Case 4.—A 32-year old white man had a spontaneous hemorrhage into a tumor in the interscapular region. The patient had multiple subcutaneous tumors and scattered areas of skin pigmentation. After he felt something "break loose" within the tumor, he went into shock and died within 12 hours, apparently as the result of bleeding into the pachydermatocele.

Case 5.—A 33-year old colored man complained of swelling of the side of his head of four days' duration. A mass as large as a grapefruit developed over the left temporal region. Evacuation of a hematoma in a gelatinous tumor beneath the temporal muscle was followed by satisfactory healing.

Case 6.—Reported by Gordon,[38] 1932:

A 44-year old white man had, at the ages of 24 and 32, developed hematomata in a neurofibroma on the right cheek. Three weeks before he was seen, he again struck his right cheek and a massive swelling occurred. The patient expired during operative removal of the hematoma and the greater portion of the tumor. Autopsy showed a number of tumors in the dura mater, in the substance of the right cheek, in the anterior wall of the stomach, and along the abdominal sympathetic nerve trunks.

Case 7.—Reported by Brunner,[39] 1936:

A 32-year old hotel employee had a spontaneous hemorrhage into a large tumor on the right buttock. After evacuation of the hematoma, rapid growth occurred in the tumor (malignant change?).

SUMMARY AND CONCLUSIONS

The manifold aspects of multiple neurofibromatosis have been reviewed in brief, with illustrations from our experience, and two of our cases with unusual surgical complications have been reported in detail. In controlling this disease we are impressed with the need of recognizing that the condition frequently is hereditary; that individuals showing the slightest evidence of involvement should be informed of the familial nature of the malady, and that they should also be advised against having children. There is a definite need to recognize and to study the mild type of the disease. More detailed studies of families so affected may help to determine the mode of its transmission.

The surgical complications in neurofibromatosis should be recognized early and appropriate treatment instituted.

These complications fall readily into three groups. The first is illustrated by those patients with complaints resulting from pressure of neurofibromata upon important structures. Whenever possible, these benign growths should

be removed. The second consists of those individuals who develop a malignant lesion at one or more points along a nerve trunk. Although there is no satisfactory treatment of these malignant growths, radical extirpation of the tumor (or amputation) followed by supplementary roentgenotherapy is the procedure usually advised. Into the third group fall those cases of neurofibromatosis with hemorrhage into a pachydermatocele. The treatment of choice is to administer adequate transfusions, evacuate the hematoma and remove the gelatinous tumor into which the bleeding has occurred.

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DISCUSSION.—DR. GEORGE J. HEUER (New York, N. Y.): Doctor Hart in his interesting discussion of von Recklinghausen's disease has grouped the surgical complications of this condition as those arising from hemorrhage into the large, so-called pachydermatoceles, from tumors, usually neurofibromata, implicating or compressing important structures in the various cavities of the body and of the extremities and from malignant degeneration of certain of the tumors occurring in this disease. With regard to the first named complication, we were the first, I believe, to describe an instance of recurring, serious hemorrhage into the large tumors of von Recklinghausen's disease; and since this original observation, have seen three additional examples. The seriousness of this complication is illustrated by our experience; for of the four cases, one died from hemorrhage into the tumor and one had such serious hemorrhages that blood transfusions alone saved his life. The nerve tumors of the neurofibroma group may, of course, occur along the course of intracranial, spinal or peripheral nerves; and not infrequently they give rise to symptoms which require surgical removal of the tumors for their relief. Both these tumors and the skin tumors seen in von Recklinghausen's disease may undergo malignant change, although this complication is rare in my experience. Such malignant tumors present the same indications for treatment as other tumors.

A serious complication in this disease, to which Doctor Hart has not referred, is infection in the large tumors (pachydermatoceles) of von Recklinghausen's disease. If one is familiar with the curious myxomatous tissue making up these tumors, he can visualize the rapidity of spread of an infection and the difficulties, surgically, of coping with it. We have observed one case. The patient developed a small ulcerated area of the skin over a pachydermatocele, presumably the portal of entrance of the infection. The infection spread throughout the large tumor with great rapidity. Its size increased greatly, the skin over it became red and hot, the entire tumor was tender. For 35 days, the patient's temperature was elevated, rising at times to 106° F.; his pulse rose to 144, his leukocytes varied between 25,000 and 40,000. He was, throughout the period, very ill. At no time did the infection proceed to abscess formation; and fortunately, after a serious siege of illness, the patient recovered.

As another, perhaps unique, observation in this disease, I should like to record the occurrence of a large myxomatous tumor within the thorax in all respects similar to the large external pachydermatoceles. The patient, a woman, age 41, entered the New York Hospital complaining of pain in the chest and shortness of breath. She presented the three major characteristics of von Recklinghausen's disease, pigmentation of the skin, skin tumors of the

fibroma molluscum type and subcutaneous tumors of the extremities believed to be neurofibromata. Roentgenograms of the chest showed an enormous shadow which completely occupied the right hemithorax except for a small area at the apex. The heart and mediastinum were dislocated to the left. A diagnosis of intrathoracic lipoma was made and operation performed March 16, 1939. On exposure, the huge tumor appeared to be encapsulated but the supposed capsule proved to be the visceral pleura. The pleura was split and the tumor within it completely removed. It weighed 8½ pounds and measured 34x29x10 cm. in its various diameters. It was composed of gelatinous, myxomatous tissue resembling that seen in the external pachydermatoceles of von Recklinghausen's disease. Dr. N. C. Foot describes the microscopic appearance of the tumor as follows: "A Cajal impregnation of this enormous tumor is extremely interesting as it brings out the morphology of the myxoblasts in the most unusual fashion. Microscopic fields which show only small nuclei in the ordinary H. and E. and Masson stains, show in these impregnated sections a profusion of stellate and spider-like myxoblasts which anastomose with one another and have a startling resemblance to the spider-cells seen in the central nervous tissue. There are, however, no nerve fibers or anything to indicate true nervous origin of this tumor. Many of these cells send anastomosing processes around the capillaries in exactly the same manner as those seen in the astrocytes of the brain. The results with the Cajal impregnation indicate that this tumor is more in the nature of a rather undifferentiated myxoma than a myxosarcoma." This patient has made a satisfactory recovery.

Dr. Kellogg Speed (Chicago): As outlined by Doctor Hart, this disease is very easily overlooked by physicians, but I may add, more easily recognized by dermatologists. The patients usually seek surgery on account of the size or position of one of the tumor masses which may involve a large nerve trunk by invasion pressure or present cosmetic complications. In the differential diagnosis, I have met stumbling blocs in an effort to distinguish between fibroma or fibromyxoma of the extremities, supernumerary nipples, periosteal fibrosarcoma, cystic osteitis and retroperitoneal tumors with myxomatous characteristics.

At the Presbyterian Hospital, Chicago, and from my own records, I may report 14 instances of von Recklinghausen's disease, five with definite familial history, three with sarcomatous degeneration of one area, three involving bone changes, one mistaken for periosteal fibrosarcoma and one cystic in type, recurring slowly after two attempts at removal locally. Autopsy was performed upon two patients, with findings of metastases (after sarcomatous degeneration) in lungs and vertebrae. In two of my own fatal cases, the disease, having become malignant in the thigh, invaded the peritoneal cavity and spread via the periaortic lymph channels, proving that the peritoneal, as well as the thoracic or cranial cavity may become involved. Errors in diagnosis seem to follow incomplete examination of the patient's fully bared body. I am also convinced that many of the unclassified retroperitoneal tumors, malignant and possibly myxomatous in consistency, take origin from unrecognized neurofibromatosis.

Dr. Max M. Peet (Ann Arbor, Mich.): I wish to add one note of the very interesting intracranial complications which may occur with von Recklinghausen's disease. We all know of the rather frequent occurrence of neurofibromata on the eighth nerve, and also the association with meningiomata. Other types of tumors of the central nervous system may also be associated with von Recklinghausen's disease. We had one patient who, in addition to

generalized peripheral neurofibromata, had acoustic tumors, and a very large meningioma in the occipital region with evidences also of meningiomata of the spinal cord. This patient died from pneumonia, and at autopsy, 17 meningiomata were found along the course of the spinal cord and numerous intracerebral and spinal gliomata. Dr. Percival Bailey, in studying the sections, found every known type of tumor involving either the central nervous system or the peripheral nerves that he had ever seen. The patient had every type of glioma. In fact, inside of certain large gliomata, in this brain were other gliomata of an entirely different character. In other words, this man had every type of tumor that could occur peripherally or centrally in the nervous system. We have seen two similar cases since.

Dr. Edwin R. Schmidt (Madison, Wis.): I wish to add six other cases, that are being reported elsewhere. In this subject, I should like to call attention to a thing which the speakers have brought out; namely, the importance of recognizing the *café au lait* spots in early cases, because the large number of cases that are being reported are usually late, when pressure symptoms have manifested themselves and surgery is difficult.

These six cases have all started in the optic nerve, and there has been great difficulty in making an early diagnosis. If the diagnosis is made earlier, then surgery is going to be more effective.

Dr. Deryl Hart (closing): Doctor Schmidt brought up the matter of early diagnosis. I think the most important single factor in the control of neurofibromatosis is early diagnosis, so that we can impress upon the patients the familial character of the condition and to urge upon them the undesirability of passing this on as will occur if they have children.

THE EFFECT ON THE BONE MARROW OF DISRUPTION OF THE NUTRIENT ARTERY AND VEIN*†

CHARLES HUGGINS, M.D., AND EUGENE WIEGE, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY OF THE UNIVERSITY OF CHICAGO, CHICAGO, ILL.

THE NUTRIENT VESSELS in the shaft of the femur in rabbits were disrupted at operation and the bone marrow studied at subsequent time intervals of four to 88 days. The nutrient vessels are relatively small and are vulnerable to injury by trauma and operation. The sequelae of such an injury and the nature of repair in the marrow have not been described.

One of the theoretic considerations in these experiments was the comparison of the extent and position of the necrosis with the natural central fat core pattern of the femur. In the extremities of man, the dog, the rabbit, and other mammals, there is frequently seen a pattern consisting of a large central core of yellow marrow surrounded by a peripheral bark of red marrow in contact with the bone;[1] this pattern is seen in regions of centripetal marrow regression in normal growing and adult animals, most frequently in the shaft of the femur, and its cause is unknown.

The blood supply of the femur in the rabbit has the usual small epiphyseal and periosteal arterial twigs, and in addition three arteries supplying the shaft. The largest of these, the main nutrient artery of the shaft, arises from the lateral circumflex artery near its origin from the femoral artery.[2] It courses downward and posteriorly to enter the nutrient foramen on the medial aspect a short distance below the lesser trochanter just anterior to the dense tendinous insertions of the short adductor muscles. Moore and Corbett[3] stated that ligation of the nutrient artery diminished the amount of callus in experimental fractures, but this was denied by Houang,[4] who found that fractures healed as well after section of the nutrient artery as in the control limb. Johnson,[5] in an ingenious series of experiments on the tibia in dogs, found that the nutrient arteries are the most important osseous vessels and maintain viability in the medulla and inner half of the cortex. Kistler[2] injected large carbon particles into the nutrient artery, producing severe infarction of the marrow with subsequent connective tissue reaction. He found that interference with the blood supply to the femur in rabbits by rupture of one or more nutrient vessels did not produce infarcts or stimulate reactionary changes except in one rabbit. Brunschwig[6] elevated the periosteum between the epiphyseal plates, thus severing all blood supply and drainage; in growing dogs this resulted in extensive marrow infarction in the shaft, but in adult dogs with closed epiphyseal plates infarction was not observed.

* Aided by grants from the Fenger Memorial Fund and the Douglas Smith Foundation for Medical Research.

† Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

Method.—In 18 rabbits, seven adults and 11 with open epiphyses, the main nutrient vessels of the femur were interrupted 23 times, under ether anesthesia and aseptic precautions. An incision, 3 cm. in length, was made just below the inguinal ligament; the quadriceps muscle, just lateral to the femoral vessels and nerve, was separated in the direction of its fibers by blunt dissection until the femur was reached. The principal nutrient vessels were easily seen just anterior to the tendinous insertion of the short rotator muscles just below the lesser trochanter and interrupted either by ligature or rupture with a forceps; the nutrient canal was then inspected for completeness of operation. Closure was obtained by means of a continuous silk suture in the skin.

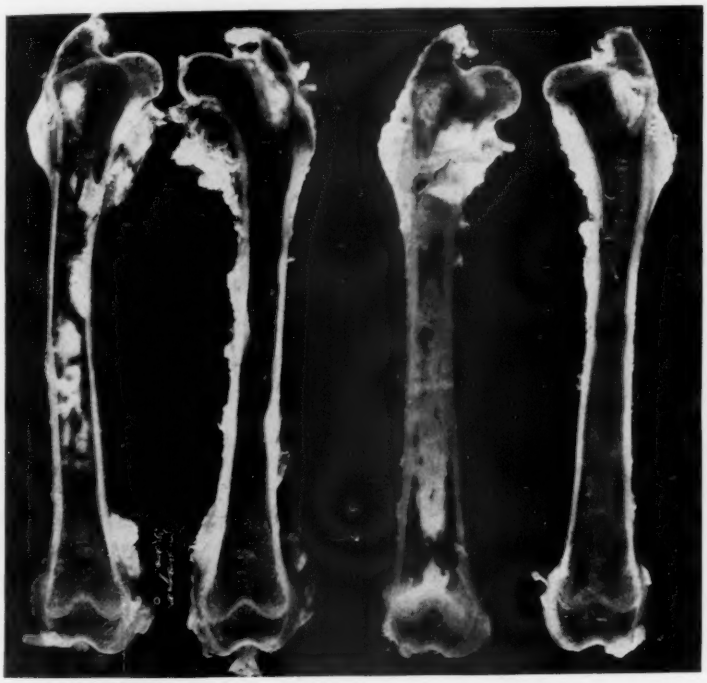

FIG. 1.—Necrosis in marrow following disruption of the principal nutrient artery. From left to right, the specimens are the experimental and control femora of Rabbit 118-0 at four days, and similar specimens from Rabbit 124-0 at seven days. Injected with ink one day before necropsy.

From three to 84 days later, 15 rabbits were injected intravenously with colloidal solutions which accumulated in the macrophages, proving the extent of revascularization. Nine rabbits were injected with a freshly prepared 20 per cent solution of Higgins' American India ink in 0.9 per cent NaCl, using 20 cc. on two consecutive days before necropsy. Three rabbits were injected with 5 cc. doses of thorotrast (25 per cent thorium dioxide by weight) on each of three consecutive days before death. Three rabbits were injected with carbon on the third and fourth postoperative day and with thorium dioxide two to three weeks later, to show the amount of vascular supply on each of these occasions.

TABLE I

Rabbit Number*	Days Since Operation	Extent of Necrosis in the Gross†	Microscopic Findings in Transverse Sections
12–C.....	4	Small	Engorged capillaries at the periphery, coagulation necrosis in middle of femur
104–O.....	4	Large	This rabbit received colloidal carbon injections on the fourth day and thorium on the thirteenth day. A large carbon-free area and a small thorium-free zone show that on the fourth day there was much ischemia, which had disappeared by the thirteenth day
112–O.....	4	Large	Much pale-staining necrosis involving center and large part of periphery of marrow
118–O.....	4	Large	Most of the area is necrotic with a partial rim of living marrow. The necrotic area is pale staining and contains no carbon. There is a slight breakdown of cells with nuclei disappearing. Slight phagocytosis
11–O.....	6	Small	Much more necrosis than appears in the gross. Much extravasation of blood between the necrotic fat cells and capillary engorgement around the periphery of necrosis. Fat cell nuclei appear normal. Many small macrophages
124–O.....	7	Very large, reaching to epiphyseal plate	The necrotic marrow is pale staining with pyknotic nuclei and much basophilic nuclear débris
79–C.....	7	Large necrotic areas in upper and lower thirds separated by living marrow	Coagulation necrosis. Macrophages and many other hemopoietic cells are creeping in at the periphery of the necrosis
77–C	9	Large	Rim of living marrow surrounds the necrotic center which is being invaded by capillaries and macrophages
125–O.....	11	Small, located in distal third of bone	Necrosis reaches the periphery of the bone at one point; it is being invaded from the side by new capillaries; myelocytes are forming
108–O.....	11	Two small necrotic areas: 1 near nutrient canal, other in lower third	Peripheral invasion by new capillaries
24–C.....	11	Small, near nutrient canal	
120–O.....	11	Large	Pale-staining cells with protein fibrils in necrotic areas. Intense peripheral capillary congestion

TABLE I (*Continued*)

Rabbit Number*	Days Since Operation	Extent of Necrosis in the Gross	Microscopic Findings in Transverse Sections
104–O.....	13	None	About 80 per cent of the section is gelatinous marrow involving the center and all of the periphery except a semilunate area. Many foreign body giant cells
115–C.....	14	Small	Two small areas of necrosis with pale cells. Much gelatinous marrow
112–O.....	22	None	Injected with carbon and thorium. Nearly normal marrow throughout. At the periphery there is much carbon as compared with the center. Much thorium throughout
19–C.....	28	None; large exostosis at site of nutrient canal	Normal appearance. There is a large clump of vacuolated cells with small fat globules; young fat cells
14–C	29	None	Normal except for bone island in marrow near nutrient canal
113–O.....	30	None	Normal appearance throughout, as in opposite control, except there is a small island of bone in the marrow center near nutrient canal
100–O.....	74	None; large exostosis at site of nutrient canal	Normal appearance
120–O.....	74	None	Normal except for small bone area in marrow center
115–C.....	77	None	Normal appearance
13–C.....	80	None	Normal appearance
12–C.....	88	None	Normal appearance

* The letters, –O, –C, designate open and closed epiphyseal cartilage plates.

† "Small" indicates an area of necrosis less than one-third of the transverse area of the marrow.

The bones were fixed in 10 per cent formalin, decalcified in 5 per cent nitric acid and sectioned transversely with a razor blade in 5 Mm. slices. Histologic sections were stained with hematoxylin-eosin.

Results.—The findings are shown in Table I. In the gross, marrow necrosis could be seen as an opaque yellow area in all specimens at 11 or less postoperative days, and in one specimen, 14 days after operation. The nutrient canals were all found to be occluded and recanalization was not observed. In all specimens later than 22 days after vascular interruption, the marrow appeared in the gross similar to that in the contralateral unoperated femur. The extent of the necrosis was variable. In the series less than 12 days, the necrosis was small five times and large seven times. In three cases, the marrow infarction was discontinuous, consisting of two necrotic zones in the shaft separated by normal marrow.

The center of the marrow was involved in the necrosis to a greater extent than the periphery. In no case was the entire transverse section of the marrow necrotic and there was always at least a partial rim of living marrow adjacent to the bone in some part of the section. The necrosis, however, was not confined to the center of the marrow and in every case involved the periphery of the marrow reaching to the bone in at least one area. In three cases, these were teat-like exostoses containing marrow at the site of the old nutrient canal. No other osseous changes were detected.

On microscopic examination, the necrosis was characterized by pale-staining cells, whose outline was maintained for about one week, and later, a pyknotic appearance of the nuclei with accumulation of small basophilic bodies resembling nuclear débris. There was a complete absence of inflammatory exudate. The spaces between fat cells early became filled with a fluid rich in protein, staining like fibrils. In most of the sections there was an intense capillary engorgement in the living marrow adjacent to the necrosis. Megakaryocytes and fat cells stained well, longer than other cells in the necrotic zones, but shrunken nuclei were evidence that these cells were dead. The specific leukocyte granules persisted longer than their nuclear material, especially in the eosinophile series.

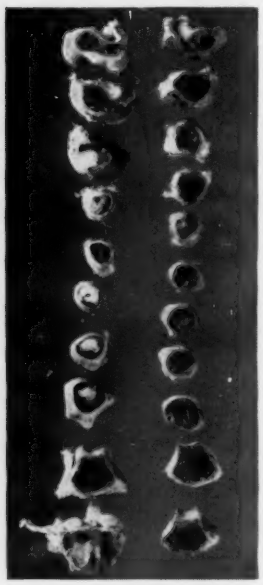

FIG. 2.—Transverse sections showing marrow necrosis following nutrient vessel interruption at nine days (Rabbit 77-C). Left, the infarcted marrow; right, the unoperated control.

Recovery was apparent four days after operation. The first apparent sign was infiltration of the periphery of the necrosis with more or less radially arranged new capillaries and macrophages. The central part of the necrosis was the last to persist and remained free of the injected particulate matter longest. Along with the new capillary and macrophage infiltration (Figs. 3 and 4), many other marrow cells and many multinucleated foreign body giant cells infiltrated the periphery of the necrosis. There was only slight histologic evidence of the disposal of necrotic marrow by the invading new tissue by phagocytosis, and few phagocytes contained unclear material. There was no evidence of lysis. An interesting finding was a lack of fibroblast formation.

From the thirteenth to the twenty-second day after operation, there were seen large areas of gelatinous marrow, an edematous loose fibrillar bone marrow (Fig. 5) with isolated single or small clumps of hemopoietic cells in comparison to densely accumulated clumps of myelopoietic cells seen in the normal condition. This gelatinous marrow was not seen after the twenty-eighth day and may be interpreted as a replacement stage in bone marrow formation. Small islands of bone occurred in the marrow substance in three specimens at 29, 30, and 74 days; this bone was located in the neighborhood of the nutrient

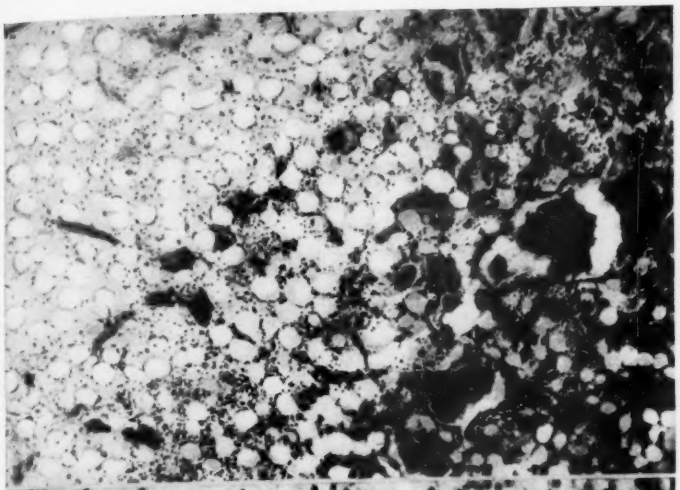

FIG. 3.—The junction of the anemic marrow infarct (upper left) with normal marrow (Rabbit 11-0, six days). (×105)

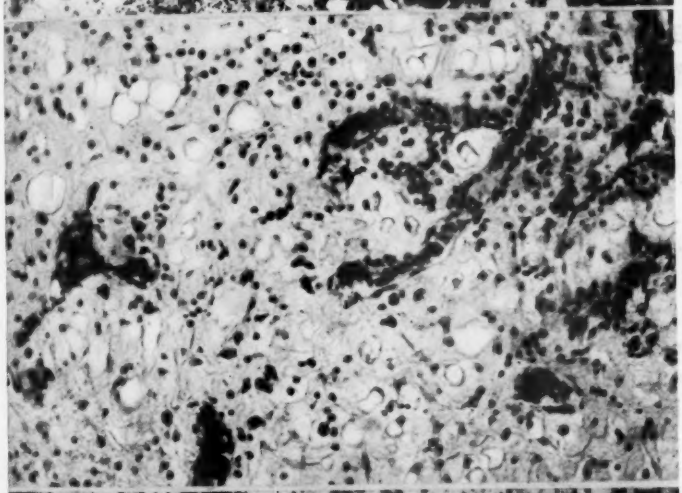

FIG. 4—The junction of the marrow infarct with normal marrow at 11 days (Rabbit 125-0) showing invasion by new capillaries, macrophages, and myelocytes. India ink injected one day before death. (×325)

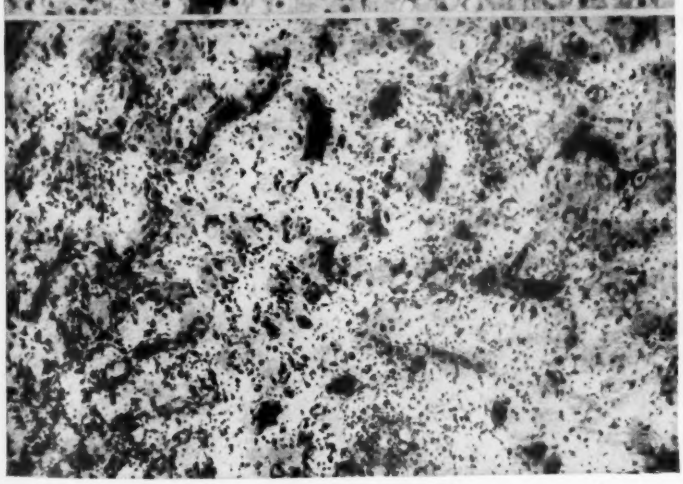

FIG. 5.—The gelatinous marrow stage of marrow repair after nutrient artery disruption at 13 days (Rabbit 104-0). Normal marrow is seen in the lower left corner. (×115)

canal. Since bone is consistently absent from the marrow of the shaft of the rabbit femur, this finding is of significance.

Discussion.—Necrosis of the bone marrow always occurred following interruption of the main nutrient vessels. While the same general appearance obtained, there were quantitative differences in the rabbits. Differences in the extent of necrosis undoubtedly can be related to differences in periosteal and articular blood supply in individual femora. The location of the necrosis shows well the area of bone marrow supplied by the nutrient artery, which is mainly the center of the marrow. A theory that the central fatty core of normal extremity marrow is related to decreases in nutrient artery function is thus supported in part by the findings, but a discordant note is struck by the observation that the necrotic area always reaches the bony wall at one point.

In all cases, complete repair occurred in the bone marrow. Study of the nature of the reparative process was enhanced by the use of injected colloids, showing vascularity at certain time intervals. Bone marrow necrosis was found to repair by a creeping substitution process from the peripheral living marrow. Between nine and 28 days, the presence of gelatinous marrow indicates incomplete regeneration of bone marrow. At 74 days and later, the marrow itself was found completely repaired and indistinguishable from the normal. There was a striking absence of inflammatory reaction to the necrosis.

The conspicuous absence of fibroblasts is of interest and may be contrasted with the findings of Kistler, who used carbon emboli, producing a much more chronic process with much fibrosis of the marrow. The necrosis occurring after simple nutrient vessel disruption apparently is a more bland process of injury than the small carbon emboli used by Kistler, which evidently obstructed smaller vessels in a diffuse manner. The repair of these marrow infarcts stands also in contrast to the repair of the infarcted spleen, an organ likewise rich in macrophages. Bloom and Taliaferro[7] found that the infarcts in the malarial spleens of canary were repaired by a process of macrophage infiltration, inflammation, scar tissue formation, and finally proliferating lymphocytic nodules formed. The inflammatory and scar stages were not observed following nutrient artery interruption in our experiments.

CONCLUSIONS

Surgical interruption of the principal nutrient artery and vein in the rabbit was always followed by bone marrow necrosis. The amount of necrosis varied in extent; the central marrow and a part of the periphery adjacent to bone were always involved. There was total absence of inflammatory exudate. An infiltrating type of repair by new capillaries and macrophages arising from the living marrow at the periphery of the necrotic zone was apparent four days after ligation, and no necrotic masses remained after 22 days. Only slight evidence of removal of the necrosis by phagocytosis was obtained. The earlier marrow repair was characterized by loose isolated cells in an edematous gelatinous marrow, but after 70 days, the marrow was indistinguishable from normal. The absence of scar tissue in the reaction to the necrosis was striking.

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CHONDRITIS OF KNEE*

WILLIAM DARRACH, M.D.
NEW YORK, N. Y.

FAILURE to cure internal derangement of the knee by removing a meniscus through a small incision, has impressed on a good many surgeons the wisdom of using an incision large enough to explore the knee joint more thoroughly. Out of 376 arthrotomies for this condition 27.1 per cent were found to have an abnormal meniscus as the only lesion. In 15 per cent the anterior cruciate ligament has been found to be partially or completely ruptured. Other common additional lesions were hypertrophied fat pads, loose bodies, synovial changes and hypertrophic spurs. There were four negative explorations.

The most commonly associated condition in this type of knee has been an alteration of the articular cartilage covering the femur, patella and tibia. The first evidence seen is a change in color and firmness. Instead of a bluish white, the cartilage looks yellow. It feels softer when pressed with a blunt instrument and when the latter is moved along the surface, the cartilage will roll up in front of it. Later it becomes fissured and frayed and tongue-like processes can be lifted up. Detached small fragments will be found lying about the joint cavity, or larger pieces up to two centimeters in diameter will be found, either free or partially attached. In the more advanced cases, the condyles or patella will be largely denuded of cartilage over small or large areas. Sometimes these areas will be covered with shining fibrous tissue, either smooth or granular in appearance.

In the large majority of instances this condition involves only the superficial portion of the articular cartilage and rarely does one see the underlying bone exposed. Occasionally, a large, deep crater is encountered, extending into the bone, and a corresponding loose body may be found somewhere in the joint. It would seem proper only to apply the term osteochondritis to this latter type, if at all.

The sites where this condition was found most frequently were, in order, the dorsal surface of the patella, the anterior surfaces of the femoral condyles, the surface just above the intercondyloid notch, the under surface of the femoral condyles, the side walls of the notch, and the upper surface of the tibia. The involved areas are usually found on opposed surfaces, *i.e.*, patella and anterior surface of femoral condyles, or lower surface of the latter and tibia. Fifty-one per cent of the cases showed involvement of the articular cartilage. In 6.8 per cent of the cases where it was present, it was the only demonstrable lesion.

The most frequently encountered associated lesions found were meniscus alone in 76, meniscus and torn cruciate ligament in 31, loose body in 18,

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

meniscus and loose body in 14, cruciate ligament alone in seven instances. Among the less common lesions found were three benign tumors (lipoma of fat pad, hemangioma of fat pad and lipoma arborescens), rheumatoid arthritis in two cases and extensive adhesions in two instances.

When this condition has been found, it has been our custom to shave off with a knife or sharp gouge, the affected cartilage, leaving as smooth a surface as possible. In eight cases we have had the opportunity of seeing at a secondary operation the late result. In six instances the areas were covered with shining, fibrous tissue either smooth or granular; in one this had occurred in the original lesion but new areas had appeared and in the other the original areas had deepened and enlarged. When this condition exists the return to normal function is distinctly slower than in the cases without this complication. This applies especially to joint fluid.

Although 26 of the cases were found in patients under age 20, the average age of the chondritis cases was 33, as compared with an average age of 25 of the cases without chondritis.

Because of its frequent association with other traumatic conditions of the knee, because it usually only affects the superficial portion of the articular cartilage, and because it generally appears on two opposed surfaces, we believe that this lesion is a response to trauma rather than the result of a general condition or to some interference with the subjacent blood supply. The term chondritis, therefore, seems more suitable than osteochondritis.

Discussion.—Dr. Kellogg Speed (Chicago, Ill.): In my recent experience with 300 consecutive injuries of the knee, excluding fracture, there have been found, upon examination or by operation, 25 instances of osteochondritis of the knee including the dissecans type, presumably existing before the trauma sustained at the time of the complaint of injury. Sometimes this condition within the knee has been completely unknown to the patient. In other instances, I have believed, particularly in some situations where compensation was sought, that the patient was aware of a prior knee joint disability and awaited some accidental trauma to capitalize it.

The onset of osteochondritis may be insidious—my youngest patient was age 18, the oldest 62. The condition is often ushered in by sudden hydrarthrosis, which seldom shows blood upon aspiration and which may subside under rest or immobilization. Sometimes locking and simulation of derangement of a semilunar cartilage may be an initial symptom. A careful roentgenologic examination may show loose bodies or those about to loosen, usually from the articular surface of the femur, but in some instances, in spite of the roentgenogram, operation may be undertaken under a diagnosis of semilunar cartilage injury and the true situation exposed only after the joint is opened for inspection—or overlooked if the incision is not large enough to show all the possibilities of changes within the joint.

The treatment may be nonoperative, where there are no free, loose bodies which may impinge between joint surfaces. Immobilization for a few weeks may permit a quieting down of the synovitis and absorption of the effusion. Recurrence of symptoms usually occurs eventually. Lasting cure may be obtained by operation. The choice of approach to the joint may be governed by roentgenologic findings or the absence of freely moving, detached bodies within the joint. One must not make the error, however, of believing that

the roentgenograms ever tell 100 per cent of the story of bone or cartilage change—in my experience it averages about 40 per cent.

For locally loose, and about to wander, pieces of cartilage-bone, a small incision, usually the Jones hockey-stick type, may suffice for removal of all threatening masses. If there are true loose and wandering bodies, bold exposure of the joint by a para- or midpatella incision may be used. For young and very active individuals or athletes, I really prefer the split patellar incision because it permits earlier and safer active use of the joint. If there are diffuse changes in the synovia with thickening, jelly-like joint contents with loose bodies and joint crepitus, I employ complete synovectomy followed by early postoperative passive and active motion. No knee joint thus treated by me has failed to be benefited in varying degrees. In the small, pure and early dissecans type, I do not believe in paring the cartilage edge as may be done in older and long standing instances. When great deformity and disabling pain persist in the joint, resection of the knee promises relief and increased use of the leg.

TREATMENT OF AVULSED SKIN FLAPS*

ALFRED W. FARMER, M.D.
TORONTO, CANADA

CASES of severe avulsion of skin occur frequently in civil practice. Four such instances are herewith reported with a new method of treatment. Three of these followed automobile accidents, and one a domestic wringer injury.

Technic of Treatment.—The method of treatment consists first in the *excision* of all the avulsed skin. The assistant treats the traumatized area in any way thought desirable. This usually consists in a thorough cleansing and débridement. The cleansing of the raw area is performed with aseptic rather than antiseptic fluids. Thus soap and water, and saline are the solutions of common choice. The avulsed skin is then treated by removal of all the subcutaneous fat. It is necessary to do this thoroughly, although it is a tedious procedure. Holding the skin on a firm, flat surface, the fat is removed by scraping, or by cutting with curved scissors, well into the dermis. The skin is then sewn accurately back into the position from which it was removed. Quilting sutures are used also, and the graft is perforated with numerous small stab wounds. The primary dressing is of normal saline. Firm pressure is obtained by bandaging, and a plaster encasement insures immobility. The dressing is changed in ten to 14 days, unless there is some special indication for an earlier examination.

ABBREVIATED CASE REPORTS

Case 1.—G. N., male, age 10, was admitted in June, 1936, following an automobile accident. There was a compound fracture of the fibula, near the ankle joint, and a very severe laceration of the soft tissues of the leg and lower third of the thigh. The skin and subcutaneous tissues from the junction of the middle and lower thirds of the thigh to the ankle joint were torn free from the deep structures. The skin was also lacerated and abraded. It was decided that the upper and lower portions might possibly live, due to circulation through the upper and lower ends, but that the superficial tissues from the knee to within three inches of the ankle had no chance to survive. They were, therefore, removed. The area, which was very dirty, was cleansed in a routine fashion. The skin and subcutaneous tissues, which had been removed, were then made into a full thickness graft by careful excision of all the fat. This free graft was replaced in the same position from which it had been taken, sewn about the edges and fixed with quilting sutures. A drain was left in place, as the whole area was very dirty on admission.

The postoperative condition is shown in Figure 1. A fenestrated plaster encasement was necessary because of the fracture. There was a considerable amount of infection, but despite this, a large part of the full thickness graft lived (Fig. 2). The superficial tissues of the lower third of the thigh died, due to poor circulation from above. It was thought later that this skin also might have been made advantageously into a full thickness graft. This area was covered with partial thickness grafts, and the final result is shown in Figures 3 and 4.

* Read before the American Surgical Association, Hot Springs, Va., May, 11, 12, 13, 1939.

FIG. 1.—Case 1: Immediate postoperative appearance. The fenestrated, immobilizing plaster encasement was necessary because of a fracture.

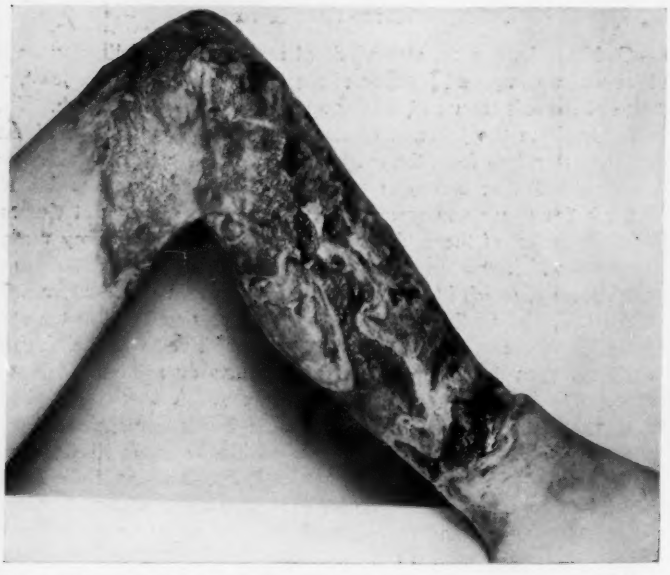

FIG. 2.—Case 1: Showing the appearance about ten days from the time of the accident.

FIGS. 3 and 4.—Case 1: Front and side views of the final result.

Case 2.—This patient was operated upon in association with Dr. W. S. Keith. B. M., female, age 7, was admitted in October, 1937, following an automobile accident, in which she had sustained laceration of the soft tissues of the left leg. The skin

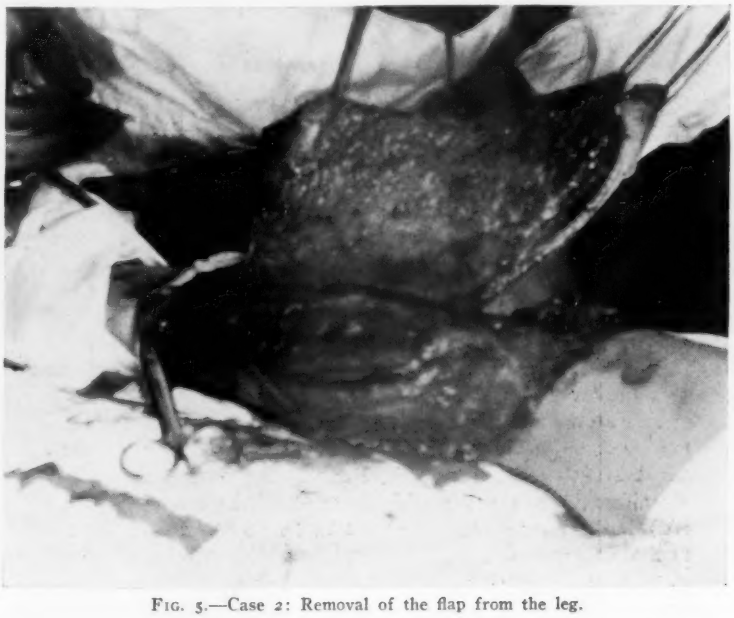

FIG. 5.—Case 2: Removal of the flap from the leg.

and subcutaneous fat were separated from the deep tissues, from above the knee region to about three inches above the ankle. They had retained an attachment along the medial aspect of the leg only, over a width of about two inches. The loose tissues were

FIG. 6.—Case 2: Return of the flap in the form of a free, full thickness skin graft.

FIG. 7.—Case 2: The result two weeks after admission.

cut free, where it was considered that they would not live if left in place (Fig. 5). A full thickness free graft made of this skin was replaced exactly as removed (Fig. 6) and sutured accurately into position. Dressings were applied and left without disturbance

FIG. 8.—Case 2: Photograph taken two months after the accident.

FIG. 9.—Case 3: Immediate postoperative result.

FIG. 10.—Case 3: The result six months after the accident.

for two weeks. There was practically a complete "take" of this graft, with the exception of one area (Fig. 7, arrow). This was about one by two square inches in area and situated over the capsule of the knee joint. The patient was discharged from the hospital in about three weeks from the time of her admission. The result some months later is shown in Figure 8.

Case 3.—R. B., male, age 10, was admitted in December, 1937, following a wringer injury. There was a laceration of the palm of the right hand, the skin, subcutaneous fat, and fascia being separated from the deep tissues in the form of a flap, with its base above the wrist. This flap corresponded to about two-thirds of the area of the palm. The skin appeared very dirty and ragged, with no evidence of circulation, except in the immediate vicinity of the base. This patient was operated upon by the house surgeon in charge. After the usual cleansing and draping, the skin flap was removed beyond a point where circulation appeared adequate. All fascia and fat was scraped off, leaving a free full thickness graft, which was then reapplied to the hand and sutured in position. Firm pressure was applied over normal saline dressings. Because of the risk of infection in the very dirty wound, dressings were changed daily. There was a perfect "take." Figures 9 and 10 show the immediate postoperative and later results. On examination of the hand at the present time, it would be impossible to estimate the nature and severity of the original injury. The functional result is perfect.

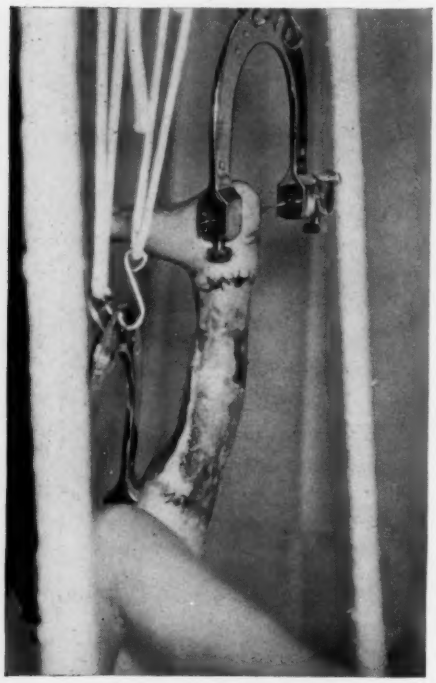

FIG. 11.—Case 4: The result two weeks after the accident.

Case 4.—G. H., male, age 18 months, was admitted in August, 1938, following an

FIG. 12.—Case 4: The condition some months following the accident.

automobile accident in which he sustained a fracture of both femora and a severe laceration of the left leg, extending from the knee to the ankle. The skin and subcutaneous fat were separated from the deep tissues, except on the anterolateral aspect, and at the ankle. The skin flap was cut free, leaving a small strip on the anterolateral aspect intact (part of this died). It was converted into a free full thickness graft and reapplied. The fractured fragments were controlled by skeletal traction. The nursing problem and general care was, of course, difficult. Despite this, over 80 per cent of the graft "took." The remaining raw area was later covered with a partial thickness graft. Figures 11 and 12 show the condition two weeks and some months, respectively, following the accident.

On examination of the literature, it is possible that this removal and replacement type of operation as described may have been performed previously, more by mistake than design, and with no comprehension of what took place. For instance, Malherbe,[1] in 1898, reported a case of scalp avulsion. The scalp was disinfected, shaved and sutured back in position. The peculiarity lies in the result. This was the only case of 21 of a similar variety, reported by Davis,[2] which did not slough. From the description, one might hazard a guess that possibly this free graft "took." The grafted scalp seemed to dry up and act as a dressing. There was some pulling away at the edges and healing was not complete for over three months. The record is not clear, and if there was a "take" of this free scalp graft, then the fact has not been recognized until the present. There is no reason why such a result should not be obtained, particularly if, in view of the present understanding, some modification of the graft were made.

This article does not undertake to discuss the preparation and after-care of a full thickness graft. This has already been done many times. The results obtained in accidental wounds depend chiefly upon the factor of infection. They will vary also, to some extent, on associated injuries, which by their presence make the after-care of the graft more difficult.

SUMMARY AND CONCLUSIONS

Four cases are reported which illustrate the use of full thickness grafts as a primary measure in the treatment of accidents when a loss of superficial tissue seems inevitable. This type of graft gives a much better result than can be obtained with partial thickness grafts employed at a later date.

This method of treatment, besides saving the damaged tissues from certain death, saves also much hospitalization and gives a better cosmetic and functional result than by any other method.

REFERENCES

[1] Malherbe, A: Bull. Med., **12**, 1121–1123, 1898.
[2] Davis, J. S.: Johns Hopkins Hosp. Rep., **16**, 257–362, 1911.

DISCUSSION.—DR. JOHN HOMANS (Boston): I am particularly interested in this contribution of Doctor Farmer's, because it applies very well to the sort of plastic work which I, as an ignorant plastic surgeon, have been performing. I have been making very wide flaps indeed, in trying to remove the subcutaneous tissues in elephantiasis of the legs. It occurred to me there was no

use in saving any fat in these flaps, so that I now make them almost entirely of skin. I cut off very carefully, with a sharp knife, all of the subcutaneous tissue (except at the very base of the flaps) and then replace the skin thus prepared upon the muscle, or whatever is left underneath.

I have noticed in making those flaps that, at the end of the operation, unless I have scarred the skin very carefully with a sharp knife, they turn very blue and it is almost impossible to make the sort of pressure which will keep them from suffering from the acute passive congestion, which is so fatal to these plastics. In other words, the flaps get plenty of arterial supply, but they do not get sufficient venous drainage. It would seem to me that in some cases I might well have made a whole thickness graft instead of attempting to secure some blood supply from the base of the flap itself. I have not yet used that method, but this work gives me the feeling that there is a good deal in this idea, and that it may be better, in planning flaps of a certain size, to use a whole thickness graft rather than to expect to be able to drain a very wide and thin flap.

Dr. Arthur M. Shipley (Baltimore): Last year, in Boston, I read a paper, and the two men who discussed it were totally at variance with my methods, but each was good enough to say that in spite of the fact that he did not approve of the methods which I had used, the statistics that I quoted spoke for themselves. I only arise, therefore, to say that in spite of the fact that many of us wonder why these flaps could not have been left attached, certainly the pictures presented speak for themselves and do not admit of very much criticism.

Dr. Sumner L. Koch (Chicago): Doctor Farmer is to be congratulated on the very excellent results he has obtained in these cases and for his emphasis on one very important fact, namely, that it is the immediate treatment which the patient receives that counts for so much, for it is the man who first sees the patient who has the best opportunity for securing successful results such as Doctor Farmer has obtained.

I wonder if there are not a few other factors that ought to be emphasized in this connection: The amount of trauma that has been sustained by the flap is certainly a very important one. If the flap has been crushed and if it is white and devitalized, nothing in the way of good surgery can save it. If it is not crushed and if the tissue is still viable, then gentle and kindly treatment will help to make its preservation more certain.

I believe, and I say this without any critical intent, that the flap which was attached to the leg along its entire lateral margin would have survived completely if it had only been carefully cleansed and had been sutured back in place, and if pressure had been maintained over it to avoid congestion. I would not wish to cut such a flap away, for it appeared to have an adequate blood supply, and it should live if every form of trauma could be avoided. The lesson that Halsted and all of his pupils have taught us, that living tissue is fragile, delicate substance and that it will survive if it receives kindly treatment, is much to the point.

In the second place, I would not like to scrape the subcutaneous tissue from such a flap. Both Blair and Neuhof have shown that in the use of full thickness grafts success depends upon getting a graft of skin alone, without subcutaneous tissue attached, stretching the graft under normal tension with the aid of sutures, and maintaining smooth pressure over it to prevent congestion and to prevent oozing of blood and serum underneath the graft. The best way to secure a graft of skin alone is by sharp dissection. If we scrape it, we traumatize the capillaries and make more difficult the ingrowth into the

graft of the new capillaries upon which the life of the transplanted tissue depends.

It seems to me Doctor Farmer's contribution is an important one and has a real place in that type of flap which is partially avulsed and which has only a distal attachment. Still I would not cut such a flap away, for even the distal attachment is of value. I would rather remove the subcutaneous fat from such a flap by sharp dissection, convert the flap into full thickness skin, and then lay it back in place and suture the free margin to the edges of the defect. Even the distal attachment would give some little blood supply that would help to safeguard the flap.

DR. HENRY F. GRAHAM (Brooklyn): Doctor Koch has stolen most of my thunder, but I should like to say just a word. This is a valuable contribution if it is used with the experience of years behind it, but if it were broadcast that every avulsed flap should be cut off and scraped and sewed back in place again, irreparable damage would be done to many people.

This speaker's second case, especially the one where the leg flap was shown, was the one that especially aroused my interest, because I had a very similar case some years ago. A doctor while driving an automobile knocked down a child and brought him into the hospital with a very large and very dirty skin flap, similar to the one shown; if anything, I think, more extensive. The child was in shock at the time, and nothing could be done even in the way of cleansing. He was almost pulseless. He was given morphine, and as the best procedure that we could follow, as long as we could not take him to the operating room, we lifted up the flap, saturated the entire wound and the inside of the flap with Zonite, about 1:3 dilution, and put on wet compresses, so that the whole wound was soaked in it. The flap was laid back over the Zonite compresses and other wet compresses placed on the outside; it was then bandaged up and left. After four or five hours the shock diminished and it was possible to take the child to the operating room. The wound was cleansed and the entire free edge of the skin flap was carefully cut away, also the edge of the wound from which the flap had been removed, and the entire wound underneath was cleansed also, removing all the little particles of street dirt with scissors. The flap was sutured back in place, a dressing applied, and primary union was obtained in that wound without any infection at all.

When a viable flap is present this is a better procedure than to try this full thickness detached graft, but I know that there are many cases where skin has been cut away and where we could have used this full thickness graft method, and I shall certainly try it in the future.

DR. A. W. FARMER (closing): We have thought of leaving avulsed skin flaps attached and making them into full free thickness grafts, and we have done it. The only case that we lost was one in which we did that. I do not know whether it has anything to do with pumping of arterial blood into the full thickness graft from the edge which is attached with inadequate drainage from it or not, but certainly I think, probably in my hands, it is better to detach the whole flap.

I would not agree with Doctor Koch. It is not a very nice thing for a surgeon to say carefulness is not necessary, but we have not found, with either the partial thickness or the full thickness variety of graft, that one needs to go to the degree of carefulness which would mean prolongation of the operation, *etc.*, where methods which are slightly more rough would make the operation more expeditiously performed.

We have not had any trouble with these free full thickness grafts, or other full thickness grafts done for other conditions in handling them fairly roughly.

PRESIDENT DALLAS B. PHEMISTER'S VALEDICTORY*

BEFORE closing this annual meeting, I want to thank the fellows for the great effort which they have made toward making it a success. We have deviated in two respects from the usual procedure, in that the meeting was held at a resort, and also that there have been three full days devoted to the program. The attendance has been all that we could have hoped for. One hundred thirty-seven have registered and almost surely there are some who have not registered. The attendance at the meetings has been unusually good. There have been from 75 to more than 100 present during the active periods of all of the sessions.

It was feared that the amenities of the locale might divert a good many to the golf links, but despite the fact that it has rained to-day, I am inclined to give you credit for staying with us and especially making this last half day a success. You know how, usually, in the big cities, the audience is made up almost entirely of medical students on the last half day. On this occasion we have not any medical students to attend.

Of course you well understand that the success of the meeting has been a great personal satisfaction to me.

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Walter Estell Lee, M.D.
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